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CYCLIC RESPONSE OF THE THYROID GLAND TO EXPERIMENTAL EXCITATION AND DEPRESSION

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The effect of iodine on the hyperthyroidism of exophthalmic goiter is dramatic not merely because of its striking depressant activity on the clinical manifestations of the disease but also on account of the temporary duration of its beneficial influence. Although the details of this unique behavior of iodine have been studied extensively,[1] little attention has been directed to their specific physiologic significance.

It is proposed, therefore, to present the results obtained from published and unpublished experiments on the functional activation and depression of the thyroid gland of the guinea-pig, to correlate these findings with relevant clinical and experimental data from the literature and finally to interpret them in terms of a relatively simple conception.

Such a study of the thyroid gland under diverse experimental and clinical conditions has revealed that its behavior is consistently influenced by a factor which limits its ability to respond indefinitely to any stimulus tending to disturb its functional stability.

The recognition and appreciation of this general principle by which the functional activity of the thyroid gland appears to be regulated

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1. (*a*) Starr, P.; Walcott, H. P.; Segall, H. N., and Means, J. H.: The Effect of Iodin in Exophthalmic Goiter, Arch. Int. Med. **34**:355 (Sept.) 1924. (*b*) Means, J. H., and Richardson, E. P.: The Diagnosis and Treatment of Diseases of the Thyroid, in Christian, H. A.: Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1929, vol. 4. (*c*) Thompson, W. O., and Thompson, P. K.: Exophthalmic Goiter: The Development of Refractoriness to Iodine, Arch. Int. Med. **48**:351 (Sept.) 1931. (*d*) Means, J. H.; Thompson, W. O., and Thompson, P. K.: On the Nature of the Iodine Reaction in Exophthalmic Goiter with Particular Reference to the Effect of Iodine Late in the Course of the Disease, Tr. A. Am. Physicians **43**:146, 1928. (*e*) Means, J. H., and Lerman, J.: The Action of Iodine in Thyrotoxicosis with Special Reference to Refractoriness, J. A. M. A. **104**:969 (March 23) 1935 (Dr. Means furnished me this material in a personal communication).

may yield further insight into the perplexing transitory character of the remission produced by iodine.

METHOD AND MATERIAL

One hundred and sixty-one guinea-pigs were utilized for the observations on which this study is based. Of these, 111 were used in the experiments on metabolism while 50 untreated normal animals were killed after a period of observation of from three to four weeks to control the histologic studies on the experimental animals. Of the 111 animals, 61 received injections of an alkaline extract of the anterior lobe of the hypophysis; 45 received simultaneous injections of the anterior lobe pituitary extract and sodium iodide, and 5 were given sodium iodide under experimental conditions which are indicated in connection with the detailed observations.

Determinations of the basal metabolic rate were carried out in a modified Benedict closed-circuit apparatus at 32 C., which is the critical temperature of the guinea-pig. Under these conditions there was a maximum variation in the normal basal metabolic rate among all the animals of approximately 10 per cent, while successive daily determinations on the same guinea-pig usually checked to within 5 to 8 per cent.

An increase in basal metabolic rate of more than 10 per cent was regarded as a significant change under the current experimental conditions.

EXCITATION OF THE FUNCTIONAL ACTIVITY OF THE THYROID GLAND

Relation Between the Thyroid Gland and the Anterior Lobe of the Hypophysis.—It is well established that the functional state of the thyroid gland can be greatly influenced by the anterior lobe of the hypophysis. Ablation of the anterior lobe of the pituitary gland causes a retardation of development or atrophy of the thyroid gland, as a result of which there is a significant decrease of the basal metabolic rate, while appropriate replacement therapy obviates this evidence of functional deterioration.[2]

It is also well recognized that injections of an acid or alkaline extract of the anterior lobe of the hypophysis stimulate the functional activity of the normal thyroid gland by virtue of a thyreotropic substance. Such extracts initiate metamorphosis in the larvae of axolotls, frogs and salamanders because of this induced hyperthyroidism, a state which can be measured quantitatively and detected histologically.[2]

Injections of potent extracts of the anterior lobe of the hypophysis also induce similar functional and histologic changes in the thyroid gland of birds and mammals.[2] In guinea-pigs they cause obvious hyperthyroidism which closely resembles exophthalmic goiter in man[3] and which is characterized by the following: (1) a cycle of histologic changes

2. A fairly extensive and detailed bibliography which is appended to the paper by Friedgood[3] should be consulted.

3. Friedgood, H. B.: Experimental Exophthalmos and Hyperthyroidism in Guinea Pigs; Clinical Course and Pathology, Bull. Johns Hopkins Hosp. **54**:48, 1934; J. A. M. A. **100**:1521 (May 13) 1933.

in the thyroid gland;[4] (2) a decrease in the total iodine and protein-bound iodine in the thyroid gland, simultaneously with an increase of these substances in the circulating blood stream;[2] (3) a transitory increase in the basal metabolic rate and in the basal pulse rate;[4] (4) a rapid loss of weight;[4] (5) exophthalmos,[4] and (6) undue nervous excitability.[4]

The behavior of this experimental syndrome in animals is likewise similar to that of the clinical course of exophthalmic goiter in man and is principally characterized by the occurrence of cycles in the symptomatic intensity of the malady,[3] in addition to a remarkable susceptibility to the influence of iodine,[5] albeit apparently a temporary one.[6]

Effect of Anterior Lobe Pituitary Extract on the Thyroid Gland of Guinea-Pigs.—Daily intraperitoneal injections of an alkaline extract of the anterior lobe of the hypophysis were given to the 61 guinea-pigs in this series in doses of 2 cc. per kilogram of body weight. The extent and duration of the response to the thyreotropic influence exerted by the extract were marked by wide individual variations. The majority of the animals reacted to this stimulus by a metabolic disturbance which revealed well defined periodic variations in intensity, a circumstance which deserves emphasis in view of the relatively brief period during which the extract is capable of exerting an influence on the functional behavior of the thyroid gland.

The initial departure from the normal metabolic level is characterized by a prompt increase in the rate of consumption of oxygen, starting within eighteen hours and reaching a maximum elevation varying from + 22 per cent to + 66 per cent about the seventh or eighth day of the experimental period.[7]

The rise in the basal metabolic rate, the development of the hypertrophic and hyperplastic changes in the thyroid gland, the increase in the concentration of iodine in the circulating blood and the decrease in the iodine content of the thyroid gland take place coincidentally.[4]

A striking, spontaneous remission develops in spite of, or because of, the continued administration of anterior lobe pituitary extract after the peak of consumption of oxygen has been reached in the second period of the metabolic disturbance. As a result of this phenomenon,

4. Footnotes 2 and 3.

5. (*a*) Siebert, W. J., and Thurston, E. W.: The Effects of Combinations of KI with Acid Anterior Pituitary Extracts, KI with Armour's Anterior Pituitary, and KI with Thyroid Substance upon Basal Metabolism in Guinea Pigs, J. Pharmacol. & Exper. Therap. **46**:293, 1932. (*b*) Friedgood, H. B.: The Effect of Iodin in Experimental "Exophthalmic Goiter" of the Guinea Pig, ibid. **51**:134, 1934.

6. Friedgood, H. B.: The Iodin Remission in Experimental "Exophthalmic Goiter" of Guinea Pigs, J. Pharmacol. & Exper. Therap. **53**:46 (Jan.) 1935.

7. Footnotes 3 and 6.

the basal metabolic rate returns to its original value within a period varying from one to three weeks. Sometimes, however, the rate of consumption of oxygen descends below its normal level at the end of this period, and this suggests that prolonged stimulation leads either directly or indirectly to a state of hypofunction of the thyroid gland.[3] The latter is contrary to the experience of Siebert and Thurston [5] and was not recorded by Anderson and Collip [8] in their initial observations on guinea-pigs.

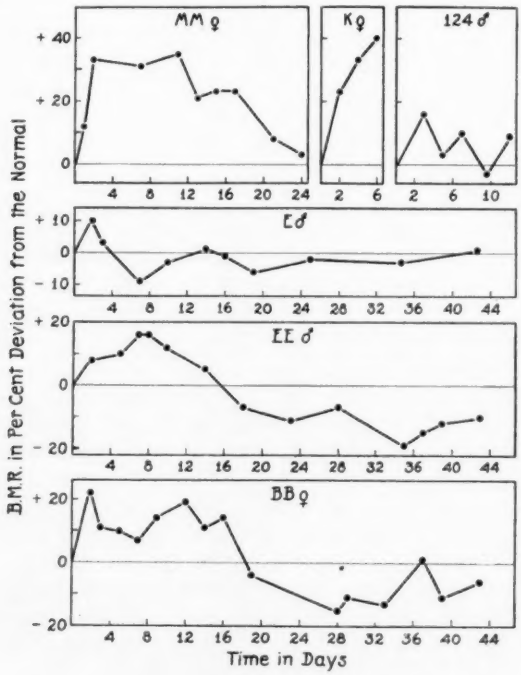

Chart 1.

The beginning of the spontaneous remission apparently takes place when the most marked histopathologic changes have developed in the thyroid gland.[3] The spontaneous involution of this parenchymal hypertrophy and hyperplasia and the reaccumulation of acinar colloid lag moderately behind the decreasing basal metabolic rate in this period.[3] By the time the basal metabolic rate has reached its normal level, how-

8. Anderson, E. M., and Collip, J. B.: Thyreotropic Hormone of Anterior Pituitary, Proc. Soc. Exper. Biol. & Med. **30**:680, 1933.

EXPLANATION OF CHART 1.

Chart 1.—All the animals were given daily intraperitoneal injections of an alkaline extract of the anterior lobe of the hypophysis in doses of 2 cc. per kilogram of body weight throughout the experimental period; most of the animals also received sodium iodide.

MM, a female control animal, received only the extract. In many instances the basal metabolic rate temporarily decreased slightly below its original level after the initial cycle of hyperthyroidism was completed.

K, a female, received 0.001 Gm. of sodium iodide per kilogram of body weight simultaneously with the extract. The iodine did not affect the course of the rapidly increasing metabolic rate.

124, a male, received 0.001 Gm. of sodium iodide per kilogram of body weight simultaneously with the extract. A brief latent period permitted a slight increase in the basal metabolic rate, after which the depressant effect of the iodine became fully established.

E, a male, received 0.11 Gm. of sodium iodide per kilogram of body weight simultaneously with the extract. The iodine completely inhibited the thyreotropic activity of the extract.

EE, a male, received 0.14 Gm. of sodium iodide per kilogram of body weight simultaneously with the extract. The depressant effect of the iodine prevented the basal metabolic rate from increasing significantly until the seventh day of the experimental period, after which the extent of its influence decreased somewhat and permitted the basal metabolic rate to increase slightly. The early remission which occurred subsequent to this brief rise in the rate of metabolism may be due in part to the continued presence of the effect of the iodine and in part to an early spontaneous remission of the hyperthyroid state such as is seen not infrequently in male animals. The experiments recorded in chart 3 suggest that the myxedema level to which the basal metabolism decreased after this remission was due to the persistence of at least a small fraction of the original influence of iodine.

BB, a female, received 0.02 Gm. of sodium iodide per kilogram of body weight simultaneously with the extract. After a brief latent period during which the basal metabolic rate increased, the iodine opposed the initial thyreotropic activity of the extract, and the rate of consumption of oxygen decreased to its normal level. This remission produced by iodine, however, persisted for only five days, after which the basal metabolic rate again began to increase. This may indicate that as the depressant effect of iodine gradually became attenuated the extract correspondingly revealed more of its hitherto latent thyreotropic activity. The usual spontaneous remission finally found the thyroid gland refractory to further stimulation, and the basal metabolic rate again returned to its normal level.

If the striking decrease in basal metabolic rate which occurred subsequent to this remission is attributed to iodine (on the basis of experiments recorded in chart 3), one must postulate that iodine retains enough power to affect the thyroid gland during the phase in which it becomes refractory to the thyreotropic substance, although its influence may have become insufficient earlier in the experiment to inhibit completely the thyreotropic activity of the extract. Such a theory assumes that the thyroid gland in the postrefractory state can develop a remarkable sensitivity toward amounts of iodine which in the prerefractory state were too minute to affect its functional activity significantly. The experimental data (chart 3 and tables 2, 3 and 4) are in accord with these theoretical considerations. As a matter of fact, from the nature of the spontaneous remission, one must conclude that the physiologic state of the thyroid gland during the period in which it is potentially capable of responding to the thyreotropic substance is fundamentally different from the condition in which it subsequently finds itself refractory to this activating influence.

ever, these regressive histologic changes are fairly complete, although the reaccumulated colloid is relatively poor in iodine.[9]

During long continued daily injections of anterior pituitary extract it has been noted in several instances that a recrudescence of this cycle of hyperthyroidism occurs after a refractory interval of approximately thirty days.[3]

A few animals (about 8 per cent of those studied) were resistant to the thyreotropic effects of the extract and revealed a highly curtailed initial increase in the rate of metabolism and a strong tendency toward an early remission.[7] Occasionally, a brief transitory secondary increase in the rate of metabolism occurred after such an aborted response. On the contrary, there were other animals, even less in number, which displayed only a negligible resistance to the extract, and after a rapid initial increase in the rate of consumption of oxygen these animals suffered several marked secondary exacerbations of the metabolic dis-

TABLE 1.—*Influence of Sex on the Thyreotropic Activity of an Alkaline Extract of the Anterior Lobe of the Hypophysis*

Maximum Basal Metabolic Rate, per Cent	All Animals, Percentage	Male Guinea-Pigs, Percentage	Female Guinea-Pigs, Percentage
Between +22 and +30.....	60	70	13.3
Between +31 and +66.....	40	30	86.7

turbance, which in one instance extended over a period of three months before the animal died accidentally.[7]

Sex may be one of the factors which play a rôle in the variable response which the thyreotropic activity of the extract elicits. Although not an invariable occurrence, the metabolic disturbance appeared to be more intense and of longer duration in female than in male guinea-pigs.[9]

The Thyroid Gland and the Basal Metabolic Rate in Exophthalmic Goiter.—The cycle of events which the thyreotropic substance of the anterior lobe of the hypophysis evokes in the thyroid gland of the guinea-pig is remarkably similar to that recorded as occurring in the thyroid gland in cases of exophthalmic goiter in man by Marine and Lenhart,[10] Wilson[11] and others.

9. Schockaert, J. A., and Foster, G. L.: Influence of Anterior Pituitary Substances on the Total Iodine Content of the Thyroid Gland in the Young Duck, J. Biol. Chem. **95**:89, 1932. Closs, K.; Loeb, L., and MacKay, E. M.: The Effect of an Acid Extract of the Anterior Pituitary on the Iodine Concentration of the Blood and Thyroid Gland, ibid. **96**:585, 1932.

10. Marine, D., and Lenhart, C. H.: Pathological Anatomy of Exophthalmic Goiter, Arch. Int. Med. **8**:265 (Sept.) 1911.

11. Wilson, L. B.: The Pathology of Nodular (Adenomatous?) Goiters in Patients with and in Those Without Symptoms of Hyperthyroidism, in Collected Papers of Mayo Clinic, Philadelphia, W. B. Saunders Company, 1922, vol. 14, p. 434.

Marine and Lenhart recognized an early developmental stage with the parenchymal hypertrophy and hyperplasia "characteristically" found in cases of exophthalmic goiter and a later involuntary or colloid phase.

Wilson described this cycle of histopathologic change somewhat as follows: (1) an early stage, with moderate enlargement of the thyroid, marked hypertrophy and moderate hyperplasia of the parenchymal cells and diffuse hyperemia; (2) an advanced stage, with marked enlargement of the thyroid, advanced parenchymal hypertrophy and hyperplasia, loss of colloid and diffuse hyperemia, and (3) a late stage, with beginning or well marked storage of colloid, decreasing hypertrophy and hyperplasia of parenchymal cells and less hyperemia. Many follicles containing colloid during the third phase of the cycle were found to be lined with flattened acinar cells.

The clinical course of the basal metabolic rate in cases of exophthalmic goiter is also similar to the cyclic type described for experimental hyperthyroidism caused by administration of an extract of the anterior lobe of the hypophysis. Many cases are marked by a progressive intensification of the metabolic disturbance until a maximum increase or crisis is reached, after which (if the patient survives) there is a period of sustained activity which spontaneously subsides over a variable number of weeks or months. There are also more chronic cases which pursue a self-limited, irregular, less intense course with a number of remissions and exacerbations.[12]

Wilson [11] indicated that there is a correlation between the cycle of histopathologic changes in the thyroid gland and the behavior of the basal metabolic rate in cases of exophthalmic goiter. His findings are similar to those recently published by me [3] for experimental hyperthyroidism caused by the administration of an extract of the anterior lobe of the hypophysis.

DEPRESSION OF THE FUNCTIONAL ACTIVITY OF THE THYROID GLAND

Behavior of the Basal Metabolic Rate After Simultaneous Administration of Sodium Iodide and the Thyreotropic Principle.—The usual increase in basal metabolic rate which is produced by the thyreotropic activity of the extract of the anterior lobe of the hypophysis may be partially or completely inhibited by simultaneous injections of sodium iodide.[13]

In general, this inhibitory influence exerted by iodine is marked by wide individual variations, but within certain fairly well defined limits

12. Barker, L. F.: Exophthalmic Goiter, Internat. Clin. **1**:1, 1924. Footnote 1b, d and e.

13. Footnotes 5 and 6.

relatively large doses of sodium iodide (from 0.1 to 0.2 Gm. per kilogram of body weight) were commonly found to be more effective than relatively small doses (from 0.0001 to 0.002 Gm. per kilogram of body weight) either in totally abolishing the expected rise in basal metabolic rate or in partially inhibiting the extent of its increase.

TABLE 2.—*Effect of Large and Small Doses of Sodium Iodide on the Thyreotropic Activity of an Alkaline Extract of the Anterior Lobe of the Hypophysis* *

	Increase in Basal Metabolic Rate				
	First Through Fifth Day,	Sixth Through Tenth Day,	Eleventh Through Fifteenth Day		
Experimental Conditions	Over +15 per Cent	Over +25 per Cent	Over +30 per Cent	Over +10 per Cent	Under +10 per Cent
Controls which received only injections of 2 cc. of anterior lobe pituitary extract	92.0	70.0	25.0	75.0	25.0
Guinea-pigs which received injections of the extract plus from 0.1 to 0.2 Gm. of sodium iodide per kilogram of body weight	23.5	11.7	0	53.8	46.2
Guinea-pigs which received injections of the extract plus from 0.0001 to 0.002 Gm. of sodium iodide per kilogram of body weight	72.2	61.1	38.4	84.6	15.4

* In addition to the more obvious differences in response elicited by large and small doses of sodium iodide, note particularly the unfavorable influence which the smallest doses of sodium iodide exerted on the course of hyperthyroidism induced by an extract of the anterior lobe of the pituitary from the eleventh to the fifteenth day of the experimental period.

TABLE 3.—*Range of Effective Doses of Iodide When It Is Administered to Guinea-Pigs Simultaneously with 2 cc. of Anterior Lobe Pituitary Extract Per Kilogram of Body Weight* *

Effect on Basal Metabolic Rate Ordinarily Increased by Anterior Lobe Pituitary Extract	Dose of Sodium Iodide per Kg. of Body Weight, Gm.	Seventeen Animals in Series (10♂; 7♀), Percentage	Dose of Sodium Iodide per Kg. of Body Weight, Gm.	Six Animals in Series (1♂; 5♀), Percentage	Dose of Sodium Iodide per Kg. of Body Weight, Gm.	Eighteen Animals in Series (7♂; 11♀), Percentage
Complete inhibition of increase	0.1 to 0.2	41 (5♂; 2♀)	0.005 to 0.090	0	0.0001 to 0.002	5.5 (0♂; 1♀)
Partial inhibition of increase	0.1 to 0.2	29.5 (3♂; 2♀)	0.005 to 0.090	100 (1♂; 5♀)	0.0001 to 0.002	33.3 (3♂; 3♀)
No effect on the expected increase	0.1 to 0.2	29.5 (2♂; 3♀)	0.005 to 0.090	0	0.0001 to 0.002	61.2 (4♂; 7♀)

* This table emphasizes the value of relatively large doses of sodium iodide as compared with minute amounts. These data also indicate that the remission produced by iodine is not an all-or-none phenomenon. The influence of sex on the remission produced by iodine cannot be judged on such limited data. It is interesting, however, to note the preponderance of male animals among those deriving the maximum benefit from the largest doses of sodium iodide.

The dose of iodine apparently also plays an important rôle in the duration of its efficacy. Sodium iodide in doses of from 0.1 to 0.2 Gm. per kilogram of body weight produced earlier evidence of its depressant effect and maintained its influence over a longer period than did doses under 0.1 Gm. per kilogram of body weight. This is probably not the only factor involved, however, for it does not explain why certain animals were refractory even to the largest doses of sodium iodide given in these experiments.

The increase in the rate of metabolism which occurred in many of the animals in this series subsequent to an initial period of depression testifies to the transitory character of the remission produced by iodine and to the constant potential stimulus which the anterior lobe pituitary extract maintains during the period that its active influence is temporarily usurped by the iodine. Indeed, the detailed data indicate that the salient characteristic of this depressant effect of iodine is its temporary duration.[6] The efficacy of iodine is most marked between the fifth and the tenth day of the experimental period. Its depressant effect, however, may persist in some measure over a variable period extending from a few days to two or three weeks.

Furthermore, the direction in which the rate of metabolism is influenced by iodine if it is given in combination with anterior lobe pituitary extract becomes obvious when the contours of the metabolic curves resulting from such experiments are compared with those for control animals which have received only the glandular extract. Such data indicate that the general behavior of the basal metabolic rate after the simultaneous administration of iodide and anterior lobe pituitary extract depends for the most part on the duration and location of the period over which the transitory depressant effect of iodine impresses itself on the cycle of hyperthyroidism caused by the administration of an extract of the anterior lobe of the hypophysis. For instance, if the effective period of the remission produced by iodine is shorter than the cycle of increased metabolism produced by a thyreotropic effect of the extract, the rate of consumption of oxygen finally increases within limits which are probably determined for a given point in the experimental period partially by the natural susceptibility of the animal to the extract and partially by the dose of iodine administered. A significant increase in the rate of metabolism, on the other hand, does not occur at any time during the experimental period if iodine depresses the metabolic disturbance until such time as the thyroid gland ordinarily becomes refractory to the thyreotropic effects of the extract. And finally, the basal metabolic rate descends to the level of hypothyroidism or myxedema in certain guinea-pigs when the depressant influence of iodine extends beyond the period during which the anterior lobe pituitary extract is capable of exerting its thyreotropic activity (*EE* and *BB*,

chart 1; chart 2*F*). All the animals which experienced a temporary iodine remission with a secondary increase in the rate of metabolism subsequently revealed a progressive decrease in the rate of consumption of oxygen which was entirely similar to the spontaneous remission seen in guinea-pigs receiving only extract of the anterior lobe of the hypophysis.

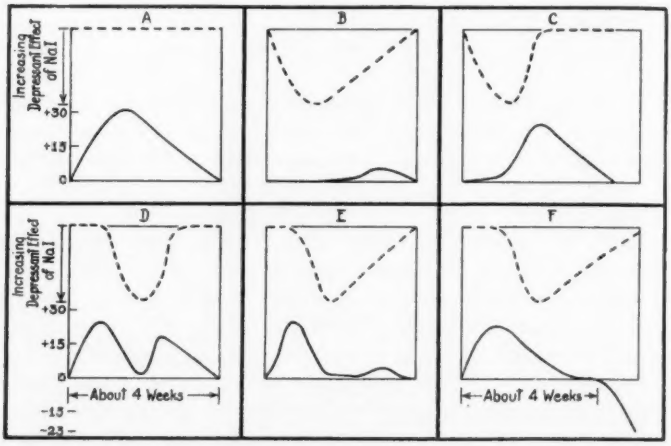

Chart 2.—The lower curves, which are represented by the solid lines, depict the actual course of events (the direction, extent and duration of percentage changes in the basal metabolic rate) in individual guinea-pigs after the simultaneous administration of iodide and anterior lobe pituitary extract. (Refer to figure 1 for the source of this material.)

The upper dotted lines signify the manner in which iodides probably exert their depressant influence in order to cause the changes in the basal metabolic rate which are so characteristic of the remission produced by iodine.

A shows that the iodine was entirely ineffective; the thyreotropic activity of the extract was therefore unopposed (compare with chart 1, K ♀).

B shows that the iodine exerted its depressant influence over a period which included the entire cycle of hyperthyroidism; the thyreotropic activity of the extract was therefore inhibited (*E*, chart 1). Certain experiments (*EE*, chart 1) indicate that the rate of metabolism may increase slightly if the depressant effect of the iodine becomes weakened considerably toward the end of its period of influence.

C, *D* and *E* show that the time of onset, the duration and the extent of the depressant effect of iodine play an important rôle in determining the behavior of the basal metabolic rate in these instances (*EE*, *BB* and *124*, chart 1). Note the slight tendency to a late increase in the rate of consumption of oxygen which may occur after the iodine relinquishes most of its depressant power.

In *F*, special attention is directed to the sequence of events which probably results when the effect of iodine persists beyond the period during which the extract maintains its thyreotropic activity. This interpretation has been substantiated by the experiments recorded in chart 3 (also *EE* and *BB*, chart 1).

Effect of Iodides in Exophthalmic Goiter.—The remission produced by iodine in cases of exophthalmic goiter in man is likewise a temporary phenomenon which ordinarily attains its maximum influence by the fifth to the tenth day, after which the basal metabolic rate usually increases more or less rapidly to equal or surpass its original level within the following few weeks.[14]

Means[16] has suggested that the excessive height to which this secondary rise in metabolic rate sometimes attains is evidence of an increasing intensity of the malady rather than an expression of the transitory duration of the depressant influence of iodine. Although this is an important possibility, the "postiodine" phenomenon might also be attributed to the fact that the administration of iodine not only depresses the functional activity of the thyroid gland but simultaneously replenishes its depleted store of thyreoglobulin.[15] As a result of this increase in the hormone content of the thyroid gland, the gland becomes capable of releasing its active secretion in larger quantities per unit of time at the termination of the limited period during which iodine depresses its functional state.

In some instances of mild exophthalmic goiter, iodides produce an unusually prolonged remission.[16] The experimental data from cases of hyperthyroidism produced by administration of an extract of the anterior lobe of the hypophysis suggest that the cycle of hyperthyroidism has approached close enough to its period of natural remission to permit overlapping of the remission produced by iodine and the spontaneous remission.

Effect of Iodides and Anterior Lobe Pituitary Extract (Thyroid-Stimulating Factor) on the Basal Metabolism After the Spontaneous Remission in Animals Which Have Previously Received Injections of the Extract.[17]—The maximum decrease in the basal metabolic rate was recorded in individual instances as 8 per cent below the normal level

14. Footnote 1a, b, c and d.

15. Gutman, A. B.; Benedict, E. M.; Baxter, B., and Palmer, W. W.: The Effect of Administration of Iodine on the Total Iodine, Inorganic Iodine and Thyroxine Content of the Pathological Thyroid Gland, Tr. Am. A. Study Goiter, 1932; J. Biol. Chem. **97**:303 (July) 1932.

16. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Prolonged Treatment of Exophthalmic Goiter by Iodine Alone, Arch. Int. Med. **45**:481 (April) 1930.

17. This experiment was originally devised to investigate the theory that depletion of the reserve of iodine in the thyroid gland is responsible for the diminishing output of its active secretion during the spontaneous remission. The results which were obtained cast doubt on this possibility and at the same time yielded further evidence of the limited period during which iodine was capable of influencing the functional behavior of the thyroid gland.

at the completion of the spontaneous remission in guinea-pigs which had received injections of only the anterior lobe pituitary extract.[17] Thereafter, the simultaneous administration of sodium iodide and anterior lobe pituitary extract (thyroid-stimulating factor) resulted in a further depression of the basal metabolic rate [18] to hypothyroid and myxedematous levels. The detailed data indicate that the depressant effect of iodine was merely temporary and that the basal metabolic rate in these experiments decreased progressively to reach its lowest level usually by the fourth day, after which there was a gradual increase in the rate of consumption of oxygen over a period of from one to more than three weeks before the original level was attained.

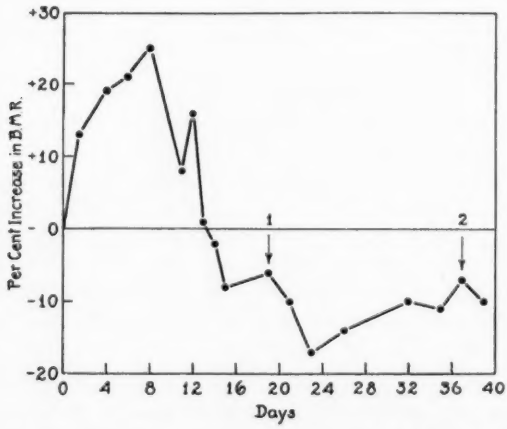

Chart 3.—This curve is composed of averaged data and is based on the 5 guinea-pigs to which reference is made in table 4.

The arrow at *1* indicates that daily injections of 0.0005 Gm. of sodium iodide per kilogram of body weight were combined with the anterior lobe pituitary extract which had previously been given alone for a period of nineteen days.

The arrow at *2* points to the time at which the dose of sodium iodide was increased to 0.175 Gm. per kilogram of body weight. The resultant decrease in the basal metabolic rate occurred in only 1 animal (from minus 13 to minus 23 per cent), while no change in the rate of metabolism was detected in the other 4 animals.

Effect of Iodides on the Basal Metabolism of Normal Rabbits.—There is a striking similarity between the results of the latter experiments and those reported by Webster and Chesney [19] and Marine, Deutch

18. Friedgood, H. B.: Studies on the Nature of the Spontaneous Remission in Experimental Exophthalmic Goiter of Guinea-Pigs, to be published.

19. Webster, B., and Chesney, A. M.; Endemic Goitre in Rabbits: III. Effect of Administration of Iodine, Bull. Johns Hopkins Hosp. **43**:291, 1928.

and Cipra [20] for the effect of iodides on the basal metabolic rate of normal rabbits. The time relations of the temporary decrease in the rate of consumption of oxygen and the period required for its recovery are almost identical in the three series of experiments. While the ultimate significance of this parallelism may not be apparent at present, the point of immediate interest is the transitory duration of the effect of the iodide in each instance.

TABLE 4.—*Temporary Effect of Iodide on the Basal Metabolic Rate of Normal Rabbits and on the Basal Metabolic Rate of Guinea-Pigs After the Spontaneous Remission*

Identification of Animal				Maximum Depression in Basal Metabolic Rate, Percentage			Day of Experimental Period on Which Maximum Depression Occurred			Day of Experimental Period on Which Basal Metabolic Rate Returned to Original Level		
Guinea-Pig (This Series)	Rabbit (Webster and Chesney)	Rabbit (Marine, Deutch and Cipra)		This Series*	Webster and Chesney†	Marine, Deutch and Cipra‡	This Series	Webster and Chesney	Marine, Deutch and Cipra	This Series	Webster and Chesney	Marine, Deutch and Cipra
125 ♂	2083	589B	♀	—24	—25	—22	4th	3d	3d	18th	30th	13th
127 ♂	2038	616	♀	—22	—19	—22	7th	4th	3d	18th (still —13%)	30th§ (still —29%)	9th (still —15%)
128 ♂	2061	622	♀	—20	—19	—21	4th	3d	1st	7th	6th	13th (still —8%)
122 ♂	2037	605	♀	—17	—16	—18	4th	3d	7th	20th (still —13%)	Between 15th and 30th	9th (still —17%)
120 ♂	2036	604	♀	—14	—11	—15	4th	2d	3d	18th	5th	13th (still —17%)§

* See chart 3 for a composite curve. The five guinea-pigs were given anterior lobe pituitary extract for nineteen days until the expected cycle of hyperthyroidism was completed. At this point sodium iodide was included in the daily injections (0.0005 Gm. per kilogram of body weight). The first day of the experimental period on which this table is based was the nineteenth day of the injections of anterior lobe pituitary extract.

† All of six animals responded with a decrease in metabolism. The percentage values were calculated from published data.

‡ Five of eighteen animals responded with a decrease in metabolism. The percentage values were calculated from published data.

§ Secondary depression.

EFFECT OF IODINE ON THE HISTOLOGIC APPEARANCE OF THE NORMAL THYROID GLAND

Gray and Loeb,[21] Rabinovitch [22] and Irsigler [23] have demonstrated that the daily intraperitoneal injections of potassium iodide in guinea-pigs and rats result in a rapid increase in the rate of mitotic prolifera-

20. Marine, D.; Deutch, M., and Cipra, A.: The Effect of Large Doses of Iodine on Heat Production in Rabbits, Proc. Soc. Exper. Biol. & Med. **24**:657, 1927.

21. Gray, S. H., and Loeb, L.: The Effect of the Oral Administration of Potassium Iodide and Thyroid Substance on the Mitotic Proliferation and Structure of Acini in the Thyroid Gland in Guinea Pigs, Am. J. Path. **4**:257, 1928.

(Footnotes continued on next page)

tion of the thyroid epithelium. The maximum effect occurs by the tenth day, at which time the number of mitoses has increased from its original level of about 200 to a maximum count of approximately 6,000 per gland (guinea-pig). The number of mitoses then begins to decrease between the tenth and the fifteenth day and practically returns to normal by the twentieth day, although the daily administration of iodide is continued uninterruptedly. A slight transient secondary rise may occur after the thirtieth day.

The oral administration of potassium iodide appears to modify the time factor in this response so that the peak of the effect of the iodide does not occur until from the fifteenth to the twentieth day, after which the number of mitoses decreases rapidly. Proliferation ceases after the thirtieth day. In addition to this temporary increase in the rate of mitosis, there are also moderate changes in the appearance of the colloid, which tends to become softer, and in the epithelium, which assumes a medium cuboid height, especially after intraperitoneal administration of iodide.

Kuschinsky [24] (confirmed by Loeser [25]) proved that these changes in the thyroid gland were produced indirectly through the anterior lobe of the hypophysis. He also demonstrated that the direct effect of iodine on the anterior lobe of the hypophysis was temporary and persisted for the same period that had been observed for the duration of its indirect effect on the thyroid gland. The functional significance of these histologic changes which are produced in the thyroid gland by virtue of the effect of iodine on the anterior lobe of the hypophysis is still to be established.

COMMENT

The data of the present investigation indicate that the response of the thyroid gland to stimulation depends, first, on the type of stimulus to which it is subjected and, second, on another factor which prevents

22. Rabinovitch, J.: The Effect of Feeding Potassium Iodide on the Proliferative Activity of the Thyroid Gland in Guinea Pigs, Am. J. Path. **4**:601, 1928; The Effect of Intraperitoneal Injection of Potassium Iodide on the Proliferative Activity of the Thyroid Gland in Guinea Pigs, ibid. **5**:91, 1929; Changes in the Thyroid Gland of the Guinea Pig Following a Period of Administration of Potassium Iodide, ibid. **6**:71, 1930; Effect of Intraperitoneal Injections of Potassium Iodide on Proliferative Activity of Thyroid Gland in Rats, Proc. Soc. Exper. Biol. & Med. **28**:394, 1931.

23. Irsigler, F. H.: Die Wirkung intraperitonealer und peroraler Jodkaligaben auf die Rattenschilddrüse, Beitr. z. path. Anat. u. z. allg. Path. **85**:221, 1930.

24. Kuschinsky, G.: Ueber die Bedingungen der Sekretion des thyreotropen Hormons der Hypophyse, Arch. f. exper. Path. u. Pharmakol. **170**:510, 1933.

25. Loeser, A.: Umstimmung der Schilddrüsentätigkeit durch Jod, Klin. Wchnschr. **13**:533 (Jan. 20) 1934.

it from responding indefinitely to the demands of any stimulus. The period during which the thyroid gland can be maintained in an abnormal physiologic state is therefore consistently limited.

Excitant and depressant stimuli induce a cycle of activity which is characterized by a departure of the gland from its normal functional level in a direction governed by the nature of the stimulus, e. g., hyper-activity or hypo-activity. After a maximum change from the initial physiologic state has been achieved and the rate of activity of the thyroid gland has been either significantly increased or decreased, a spontaneous remission occurs. The return toward the original functional level progresses in spite of, or because of, the continued presence of the stimulus. In certain instances, there is also a tendency for this regression to swing slightly beyond the initial point of departure into the opposite physiologic state, i. e., from hyperthyroidism to hypothyroidism.

These well defined relationships between stimulus and response may become somewhat more complicated if the functional activity of the thyroid gland is, to begin with, in an abnormal state (e. g., the effect of iodine on the established hyperthyroidism in cases of exophthalmic goiter and on the experimental hyperthyroidism due to extract of the anterior lobe of the hypophysis). In such instances there is apparently a summation of the two opposite forces. The result depends not only on the relative influence on the thyroid gland of the opposing stimuli but on the manner in which their transitory cycles of activity overlap (chart 2).

The total time required by the thyroid gland of the guinea-pig to negotiate its complete cycle following stimulation varies from two to about four weeks. However, the maximum deviation from the normal functional level is usually attained by the seventh day of the experimental period.

The cyclic response of the thyroid gland to stimulation may be an inherent characteristic of its physiologic organization. This does not appear to be true, however, for the effect of iodides on the histologic appearance of the thyroid gland. Kuschinsky's investigations [24] certainly indicate that the anterior lobe of the hypophysis plays an important rôle in determining the character and duration of this effect of iodide. A similar extrathyroid mechanism for controlling the unbridled activity of the thyroid gland remains a possible explanation for the refractory state which develops during the administration of the thyreotropic principle.[7]

Careful experiments indicate that this remission is not due to a progressive decrease in the potency of the extract.[8] Although there are several obvious possibilities, no cleancut evidence is as yet available to permit a final judgment in the matter.

Several experiments (chart 3) which were devised to limit the number of these possibilities suggest that depletion of the reserve of iodine in the thyroid gland is probably not responsible for this phenomenon, while other data [18] have established that the spontaneous remission is not due to inactivation of the thyroid hormone or to interference with peripheral oxidation but may be directly attributed to a decrease in the output of the calorigenic hormone from the thyroid gland.

Collip and Anderson [26] have recently published evidence on the production of a serum which is inhibitory to the so-called thyreotropic hormone. Their experimental data are convincing, but the conception of an antihormone by which they attempt to explain their results can be accepted only with reservation at the present time.

The chemically crude protein-containing extracts now in use suggest that the development of a specific antibody might directly neutralize or inactivate the injected anterior lobe pituitary extract. Furthermore, iodine is known to be a powerful antagonist of the thyreotropic activity of such extracts. It seems reasonable, therefore, to withhold final judgment on their antihormone theory until further work establishes, among other things, first, whether the antagonistic substance which they have encountered is active against similar extracts prepared from several species of mammal or whether it is specifically potent only against the extract which stimulates its production, and, second, that iodine itself has played no rôle in the phenomenon which they have described.

26. Collip, J. B., and Anderson, E. M.: The Production of Serum Inhibitory to the Thyrotropic Hormone, Lancet **1**:76 (Jan. 13) 1934.

NORMAL HEMATOLOGIC STANDARDS

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This paper presents a summary of the results of a series of hematologic studies, including all the commonly used procedures, on over 500 healthy persons of both sexes ranging from young children to adults. Details of these studies [1] together with reviews of the literature will appear elsewhere. The development of a uniform system of methods for the hematologic study of oxalated venous blood made this investigation possible. These methods are simple enough for routine clinical use, but they approach research methods in accuracy. Erythrocyte counts, hemoglobin values, hemoglobin coefficients and color indexes are reported for 626 persons; cell volumes, volume coefficients and volume and saturation indexes, for 583; reticulocyte counts, for 476; leukocyte and differential counts, for 597, and sedimentation rates, for 853. The ages of the subjects ranged from 4 years to past 30.

SUBJECTS

All the subjects lived in or near Portland, Ore., at an elevation of less than 500 feet (152.4 meters). All were white and native-born, in most instances of native-born parents. Most of the men were medical students and a few were physicians; the women were for the most part nurses, with a few laboratory technicians and medical students. The boys aged from 14 to 19 and the girls from 14 to 17 were high school students. The children were from the public graded schools,[2] orphan asylums,[2] baby homes, physicians' families and the outpatient clinic. The children of the outpatient clinic had been brought in for tonsillectomy but were found by the examining physician to present no indications for this operation. The results obtained for persons of the different social classes were at first averaged separately, but no significant differences were found. All the subjects had had a recent physical examination, and they stated at the time the blood was taken that they felt perfectly well. Tests giving atypical results were repeated, and the patient was reexamined in many instances, but unless a reason was found other than the results of one of the hematologic tests, the subjects were not excluded from the series.

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Read before the Section on Pathology and Physiology at the Eighty-Fifth Annual Session of the American Medical Association, Cleveland, June 14, 1934.

1. Mrs. Mable Wilhelm Osgood, Mr. Russell L. Baker and Miss Inez Brownlee collaborated in these studies.

2. Dr. Helen Cary and Dr. Frank Mount cooperated in securing suitable subjects from the schools and orphan asylums.

It seems justifiable to regard these subjects as representative of the healthy[3] white population of the Pacific Northwest. There is considerable evidence (table 1) that data derived from such subjects are applicable to those from other parts of this country and from Europe.

METHODS

Since the methods have been described in detail elsewhere,[4] they will be commented on briefly here. Venous blood containing 2 mg. of dry potassium oxalate

TABLE 1.—*Mean Hematologic Values for Persons of Different Localities* *

	Men				Women			
Locality	Number of Subjects	Red Cells, Millions per C.Mm.	Hemoglobin,† Gm. per 100 Cc.	Volume of Packed Red Cells,‡ Cc. per 100 Cc.	Number of Subjects	Red Cells, Millions per C.Mm.	Hemoglobin,† Gm. per 100 Cc.	Volume of Packed Red Cells,‡ Cc. per 100 Cc.
United States, East Groups I and II	61	5.40	15.8	46.6	73	4.78	14.0	41.5
United States, Midwest Groups I and II	7	5.50	16.1	47.0	15	4.89	14.3	43.1
United States, West Groups I and II	2	5.56	16.0	48.2	2	4.70	14.1	41.3
United States, South Groups I and II	16	5.40	15.6	45.7	11	4.85	14.1	43.0
United States, Midwest Haden	70	4.95	15.3		30	4.38	13.4	
United States, Midwest Haden	40	4.97	15.5	45.8	12	4.26	13.3	39.0
United States, East Emerson	171	5.44	15.1					
United States, West Osgood	137	5.39	15.8	46.4	100	4.80	13.7	42.4
United States, South Wintrobe	100	5.85	17.0	49.6	50	4.93	13.8	41.5
Various parts of the world	310±	5.50	16.2	46.0	210±	4.78	13.9	41.0
United States, South Foster and Johnson	40	5.26	15.7	46.7				
Denmark Gram and Norgaard	10	5.45	15.0	46.3	10	4.65	13.0	40.5
Denmark Bie and Möller	10	5.53	14.8	46.4	10	4.74	13.3	38.7
Germany Horneffer	40	4.96	16.0					
England, London Price-Jones	100	5.48	14.9		100	5.01	13.9	
Average for entire series	477±	5.43	15.9	47.7	369±	4.85	13.9	41.8

* Reproduced by permission of Wintrobe, M. M. (Blood of Normal Men and Women, Bull. Johns Hopkins Hosp. **53**: 118 [Sept.] 1933).
† Corrected to correspond to values obtained by the Van Slyke method.
‡ Corrected to correspond to the volume of packed red cells in heparinized blood.

3. Many reports of so-called normal values have been based on studies of patients with minor illnesses in clinics or hospitals. This practice is to be condemned. It probably accounts for some of the differences between the standards determined by my associates and me and those in general use.

4. (*a*) Osgood, E. E.; Haskins, H. D.; Trotman, F. E., and Mathieu, A.: A Uniform System of Hematologic Methods for Use with Oxalated Venous Blood: A Simplification of the Osgood-Haskins Hemoglobin Method; A Rapid Method for Determination of the Sedimentation Rate of the Red Cells with Results in Health and Disease, J. Lab. & Clin. Med. **16**:476 (Feb.) 1931. (*b*) Osgood, E. E.: A Textbook of Laboratory Diagnosis, Philadelphia, P. Blakiston's Son & Co.,

per cubic centimeter was used for all the determinations and is recommended for use as a routine because of its convenience and the greater accuracy of the results. No difficulty was encountered in obtaining blood from a vein, even with the younger children. The blood was taken at any time of the day, as in ordinary office practice.

Red cell counts were made with apparatus certified by the Bureau of Standards, Toisson's diluting fluid [5] being used. Two or more counts made on separate dilutions agreeing to within 100,000 cells per cubic millimeter were averaged.

Leukocyte counts were made in the usual manner, the average of two counts agreeing to within 1,000 cells being recorded.

Estimations of hemoglobin were made with the care employed for research by the method of Osgood and Haskins,[4] for the determination of hemoglobin,[6] which, although a simple clinical procedure, has been shown [7] to give results comparable in accuracy to the methods of Van Slyke for the determination of the oxygen capacity or the iron of the blood. Results are expressed both in grams per hundred cubic centimeters and in percentages, 100 per cent by this method being equivalent to 13.8 Gm. per hundred cubic centimeters. The cell volume was determined by centrifugation to constant volume in my cell volume tube.[8] Correction for shrinkage due to the oxalate should be made by the addition of 3.5 per cent of the volume of packed cells if one wishes to compare the results with those obtained with isotonic anticoagulants, but this is not necessary if one uses oxalated blood.

Hemoglobin and volume coefficients were calculated in the usual way,[4b] and color, volume and saturation indexes were computed from the average coefficients determined for the sex and age group to which the subject belonged. Corpuscular hemoglobin, corpuscular volume and concentration of corpuscular hemoglobin were computed according to the method of Wintrobe.[9]

The differential cell counts represent the average of two counts of 100 cells each checked with each other. These were made from the thin ends of blood smears stained with Wright's stain, a buffer solution of phosphate [9a] with a p_H of 6.4 being used instead of water.

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ed. 2, 1935, pp. 192 and 378; Relation Between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women, Arch. Int. Med. **39**:643 (May) 1927. Osgood, E. E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standards, ibid. **37**:685 (May) 1926; Tables for Calculation of Color Index, Volume Index and Saturation Index Based on Recently Determined Standards, J. Lab. & Clin. Med. **12**:899 (June) 1927. Osgood, E. E., and Wilhelm, Mable M.: Reticulocytes, ibid. **19**:1129 (July) 1934. Osgood, E. E.; Baker, R. L., and Wilhelm, Mable M.: Reticulocyte Counts in Healthy Children, Am. J. Clin. Path. **4**:292 (May) 1934.

5. Osgood,[4b] p. 408.

6. The standard is obtainable from Hynson, Westcott and Dunning, Inc., Baltimore.

7. Dowden, C. W.; McNeill, C., and McNeill, J. D.: A Clinical Study of Blood Iron and Hemoglobin, J. Lab. & Clin. Med. **19**:362 (Jan.) 1934.

8. The cell volume tube is obtainable from the Arthur H. Thomas Company, Philadelphia.

9. Wintrobe, M. M.: Size and Hemoglobin Content of the Erythrocyte, J. Lab. & Clin. Med. **17**:899 (June) 1932.

9a. Osgood,[4b] p. 411.

Reticulocyte counts were made by mixing 5 drops of oxalated blood with 5 drops of a 1 per cent solution of brilliant cresyl blue in an 0.85 per cent solution of sodium chloride and allowing the suspension to stand one minute or longer. A thin smear was made, and all the reticulocytes occurring among 1,000 consecutive erythrocytes were enumerated and the percentages calculated. Total reticulocyte counts were not determined, since Osgood and Wilhelm [4b] have shown that they are of little significance.

The determinations of the sedimentation rate [4b] were made by reading at the end of fifteen and forty-five minutes the number of millimeters that the cells had settled from a column of oxalated blood in a pipet [10] containing 1 cc. of blood at a point 200 mm. from the tip and graduated in millimeters from this point to the tip. This method has all the advantages of the Westergren method and of the graphic method of Cutler; it is simpler and more rapid and uses the same oxalated blood employed for other hematologic methods.

All the determinations were made by persons highly skilled in the use of the methods.[11]

RESULTS

The results are summarized in charts 1 to 6 and in table 2. The results of my previously reported studies [4b] are included. In addition to the average values, ranges are given which include 95 per cent of the results for healthy subjects, corresponding to a range of plus or minus about three times the probable error. There is only about one chance in twenty that a result falling outside these values is normal. It is recommended that the values within these ranges be used in interpreting results rather than those within the extreme ranges which may be seen in the charts.

It was anticipated that the results would fall into three groups: those for children, those for adolescent boys and girls and those for adults. It was found that the ages at which changes took place in the various values did not always correspond to these divisions, so normal values for each method used in the investigations are divided into groups based on sex and age (table 2) according to the observed distribution. The few subjects who were past 30 are included in the 30 year group indicated in the charts. The values given in the text and in table 2 are those recommended for clinical use; those indicated in parentheses are the actual average values.

When there were no significant differences between the sexes the results for the two sexes were averaged. Differences between the sexes

10. Arthur H. Thomas Company, catalog no. 3649-A.

11. The erythrocyte counts and determination of cell volume were made by Dr. Frank E. Trotman, Mr. Russell L. Baker and Mrs. Mable Wilhelm Osgood; the hemoglobin estimations and reticulocyte counts, by Mrs. Mable Wilhelm Osgood and me, and the leukocyte and differential counts and the determinations of the sedimentation rate, by Miss Inez Brownlee, Mr. Russell L. Baker and Mr. Howard Johnson. The calculations were all checked several times by Mrs. Mable Wilhelm Osgood, myself and others.

were found only in the values pertaining to the size and hemoglobin content of erythrocytes for persons over 13.

TABLE 2.—*Hematologic Values Obtained for Healthy Subjects in the Present and Similar Series*

	No. of Subjects	Age, Years	Sex	Average Values		Range of Values
				Clinical	Actual	
Erythrocyte count, millions	215	4-13	M & F	5.0	(5.04)	4.2-5.8
	259	14-30+	M	5.4	(5.42)	4.6-6.2
	152	14-30+	F	4.8	(4.83)	4.2-5.4
Hemoglobin, percentage	215	4-13	M & F	85	(85.90)	70-100
	259	14-30+	M	115	(114.82)	100-130
	152	14-30+	F	100	(100.80)	85-115
Hemoglobin, Gm.	215	4-13	M & F	12.0	(11.92)	10.0-14.0
	259	14-30+	M	15.8	(15.84)	14.0-18.0
	152	14-30+	F	13.8	(13.91)	11.5-16.0
Hemoglobin coefficient	215	4-13	M & F	12.0	(11.87)	10.20-13.80
	259	14-30+	M	14.7	(14.66)	12.75-16.75
	152	14-30+	F	14.3	(14.41)	12.50-16.00
Cell volume, cc. per 100 cc.	215	4-13	M & F	36	(36.02)	31-41
	46	14-17	F	36	(36.73)	31-41
	63	14-19	M	41	(40.14)	36-45
	106	18-30+	F	41	(40.96)	36-45
	153	20-30+	M	45	(44.79)	40-50
Volume coefficient	304	4-17	M & F	36	(36.31)	31-41
	173	18-30+	M	41	(40.29)	35-45
	106	18-30+	F	43	(42.83)	38-47
Color index	626	4-30+	M & F	1	(1.00)	0.85-1.15
Volume index	583	4-30+	M & F	1	(1.00)	0.85-1.15
Saturation index	583	4-30+	M & F	1	(1.00)	0.90-1.10
Reticulocytes, percentage	476*	4-30+	M & F	1.5	(1.46)	0.50-3.00
Leukocyte count	86	4- 7	M & F	10,400	(10,365)	6,000-15,000
	242	8-18	M & F	8,300	(8,342)	4,500-13,500
	269	19-30+	M & F	7,400	(7,447)	4,500-11,500
Segmented neutrophils, percentage	241	4-14	M & F	38	(37.60)	18-58
	120	15-19	M & F	48	(47.65)	25-75
	236	20-30+	M & F	54	(54.26)	33-78
Neutrophil staff cells, percentage	219	4-13	M & F	3.0	(3.07)	0-10
	378	14-30+	M & F	0.8	(0.78)	0- 5
Lymphocytes, percentage	241	4-14	M & F	48	(48.21)	21-71
	120	15-19	M & F	42	(41.91)	22-62
	236	20-30+	M & F	38	(37.76)	18-65
Monocytes, percentage	219	4-13	M & F	3	(3.08)	0.5-7
	378	14-30+	M & F	4	(4.18)	0-9
Segmented eosinophils, percentage	219	4-13	M & F	2.8	(2.79)	0-8
	378	14-30+	M & F	1.9	(1.90)	0-6
Segmented basophils, percentage	597	4-30+	M & F	0.5	(0.52)	0-2
Disintegrating cells, percentage	219	4-13	M & F	5.0	(4.89)	0-10
	378	14-30+	M & F	3.5	(3.47)	0-7
Sedimentation rate, mm. in 15 min.	853*	4-30+	M & F	..	..	0-5
Sedimentation rate, mm. in 45 min.	853*	4-30+	M & F	..	..	1-30

* The discrepancy between these values and those recorded on the charts is due to the fact that the ages were not recorded for some of the adults studied.

The erythrocyte counts (chart 1) average 5,000,000 (5,040,000) per cubic millimeter and range from 4,200,000 to 5,800,000 for children from 4 to 13 years of age. At the age of 14 the results for the two sexes diverge sharply, attaining rapidly the values for adults. The erythrocyte counts for males aged 14 and over average 5,400,000 (5,420,000) and range from 4,600,000 to 6,200,000; for females the

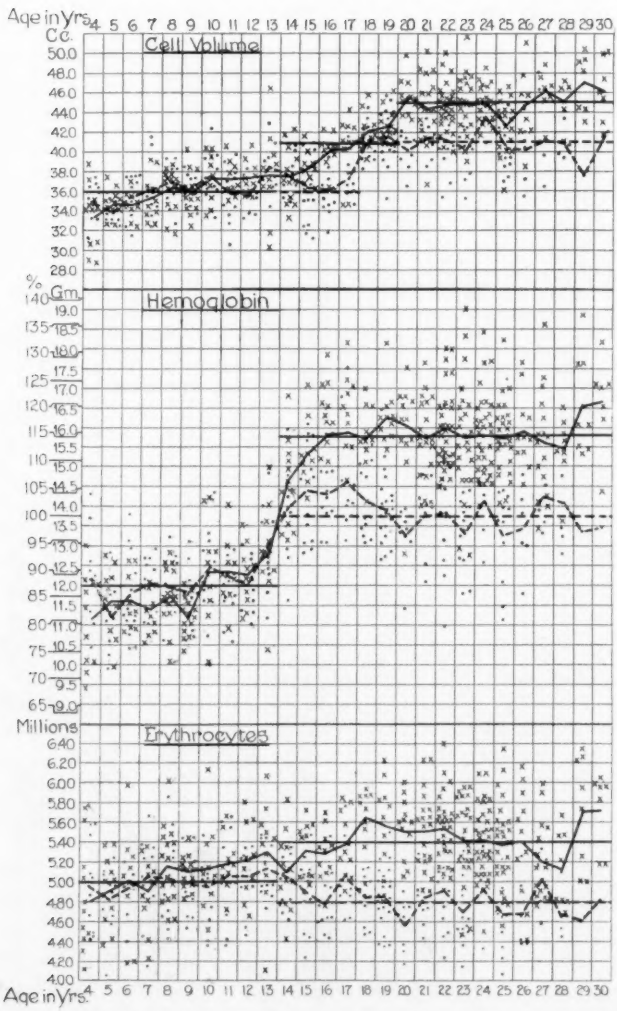

Chart 1.—Curves for the average values and the distribution of individual values for the cell volume, hemoglobin content and erythrocyte count. The values for the cell volume are expressed in cubic centimeters per hundred cubic centimeters for 328 males and 255 females; those for hemoglobin, in percentages and in grams per hundred cubic centimeters for 371 males and 255 females, and those for the number of erythrocytes in millions for persons of the same groups as those on which the studies of hemoglobin were based. In this chart and in the accompanying charts the curves for males are shown in solid lines and the individual values by crosses and the curves for females by broken lines and the individual values by dots. The values in all the studies were obtained for persons ranging in age from 4 to 30 years.

average is 4,800,000 (4,830,000), with a range of from 4,200,000 to 5,400,000. There seems to be no excuse for retaining the obsolete value of 4,500,000 for women and that of 5,000,000 for men still found in some textbooks.

The hemoglobin (chart 1) for children is lower than that for adults of either sex, averaging 12 (11.92) Gm. per hundred cubic centimeters, or 85 (85.9) per cent, and ranging from 10 to 14 Gm., or from 70 to 100 per cent. At the age of 14 the concentration of hemoglobin increases for both sexes but more markedly for boys, quickly reaching the values previously established for adults (table 1). The average value for males aged 14 and over is 15.8 (15.84) Gm., or 115 (114.82) per cent, with a range of from 14 to 18 Gm., or from 100 to 130 per cent, and for females the average value is 13.8 (13.91) Gm., or 100 per cent, with a range of from 11.5 to 16 Gm., or from 85 to 115 per cent. The only series of hemoglobin estimations for this age group of comparable size and accuracy is that of Williamson,[12] who studied 68 children of each sex aged from 4 to 15 years and 156 men and 157 women aged from 16 to 60, a total of 449 subjects compared to that of 626 reported on here. It is generally recognized that his values are accurate in relation to each other but that they are all too high.[13] If 10 per cent is deducted from his values they agree satisfactorily with those reported here.

The hemoglobin coefficient (chart 2) is the number of grams of hemoglobin per hundred cubic centimeters of blood calculated on the basis of a red cell count of 5,000,000 per cubic millimeter. The average hemoglobin coefficient for a person of the age and sex of the subject should be used as equivalent to 100 per cent hemoglobin in calculating the color and saturation indexes. It is noteworthy that the average hemoglobin coefficient for the 215 children, 12 (11.87), is considerably lower than that for adults and that the average hemoglobin coefficient for women, 14.3 (14.41), is slightly lower that that for men, 14.7 (14.66). This means that the red cells of children contain on the average about 20 per cent less hemoglobin than those of adults. The difference between the sexes in adult life is definite but not so marked as to introduce any great clinical error if Wintrobe's[9] suggestion of using the average value of 14.5 is followed. However, the tables for calculation[4b] render the use of the more accurate values simple. The

12. Williamson, C. S.: Influence of Age and Sex on Hemoglobin: A Spectrophotometric Study of Nine Hundred and Nineteen Cases, Arch. Int. Med. **18**: 505 (Oct.) 1916.

13. Notwithstanding this fact, the Newcomer hemoglobinometer is standardized so that 100 per cent corresponds to the value of 16.92 Gm. per hundred cubic centimeters obtained by Williamson for men.

difference between the average hemoglobin coefficient for children and for men and women makes it impossible to select any one value as normal for the percentage of hemoglobin. All results for hemoglobin should be reported in grams per hundred cubic centimeters and interpreted in the light of the normal values for a person of the age and sex of the patient.

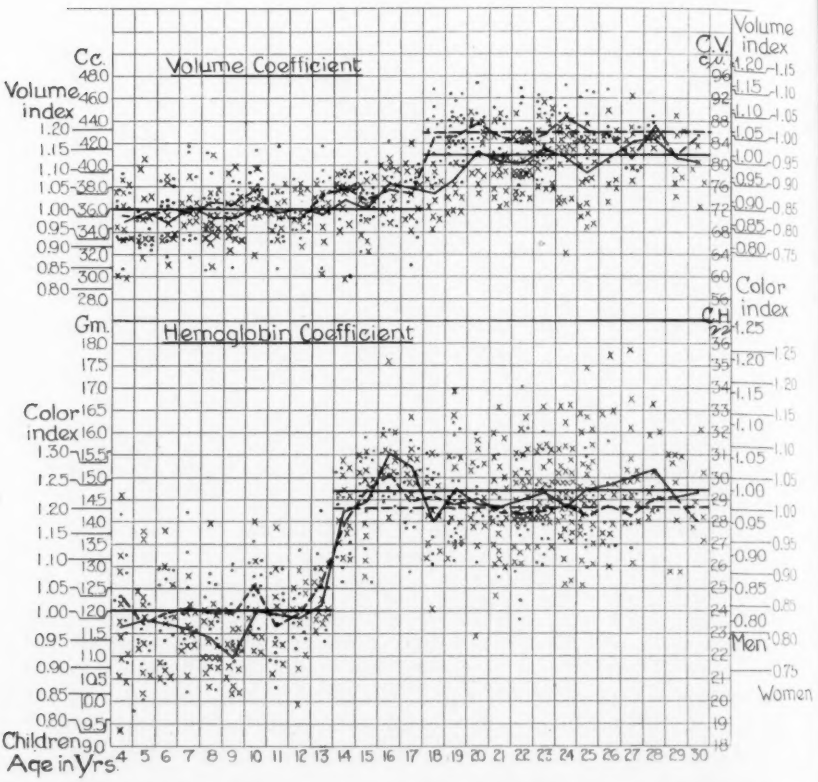

Chart 2.—Curves for the average values and the distribution of individual values for volume and hemoglobin coefficients. The values for the volume coefficient are expressed in cubic centimeters of packed cells per hundred cubic centimeters for 328 males and 255 females and those for the hemoglobin coefficient in grams per hundred cubic centimeters for 371 males and 255 females. The color and volume indexes, calculated from the hemoglobin and volume coefficients, are indicated for children and for men and women of the various age and sex groups. The corpuscular hemoglobin (*C.H.*), expressed in micromicrograms, and corpuscular volume (*C.V.*) expressed in cubic microns (*c. μ*), are shown at the right.

The cell volume (chart 1) is expressed in cubic centimeters of packed erythrocytes per hundred cubic centimeters of blood. It is much lower, with an average of 36 cc. and a range of from 31 to 41 cc. for children aged from 4 to 13 years and for girls aged from 14 to 17 than for boys from 14 to 19 and for women from 18 to 30. For women the average cell volume is 41 cc., and the range is from 36 to 45 cc. per hundred cubic centimeters of blood. For men of 20 and past the cell volume is still higher, averaging 45 cc. with a range of from 40 to 50 cc., which corresponds to the higher red cell count for men.

The volume coefficient (chart 2) is expressed as the number of cubic centimeters of packed red cells per hundred cubic centimeters of blood calculated on the basis of a red cell count of 5,000,000 per cubic millimeter. The average normal volume coefficient for the sex and age group to which the subject belongs should be used as equivalent to a cell volume of 100 per cent in calculating the volume and saturation indexes. It is interesting to note that the cells remain small, the volume coefficients averaging 36 (36.31) with a range of from 31 to 41 until the age of 17, although the hemoglobin content of the cells increases at the age of 14. The volume coefficients for women average 43 (42.83), with a range of from 38 to 47, and for men, 41 (40.29), with a range of from 35 to 45, showing that the cells of women are slightly larger than those of men.

The color, volume and saturation indexes (chart 2) for all the ages represented and for both sexes average exactly 1 and range from 0.85 to 1.15, with the exception of the saturation index, which shows a range of from only 0.9 to 1.1. The indexes were calculated from the hemoglobin and volume coefficients determined for each sex and age group. If all the indexes had been calculated on the basis of the standards for men it is evident from chart 2 that children would have a color index of about 0.82, a volume index of about 0.88 and a saturation index of about 0.93. In other words, the erythrocytes of children are, on the average, smaller than those of adults; they contain much less hemoglobin per cell and have a somewhat lower concentration of corpuscular hemoglobin. It is also evident that the color index, the hemoglobin coefficient and the concentration of corpuscular hemoglobin are but different ways of expressing the same thing. Calculation of the color index is recommended as the simplest method for comparison.

Similarly, the mean corpuscular volume expresses the same thing as the volume index or the volume coefficient. It is the average volume of the erythrocyte expressed in cubic microns. It is interesting to note in table 2 that the saturation index shows less variation within one sex and age group than the color index. In other words, the concentration of hemoglobin per unit volume of red cells remains constant.

The average concentration of corpuscular hemoglobin may be calculated by dividing the hemoglobin, expressed in grams, by the cell volume, expressed in cubic centimeters. The result is expressed in percentages. We obtained the same value (35 per cent for men) as that given by Wintrobe.[9] The value for women and for children aged from 4 to 13 years was 33.5 per cent, but we found higher concentrations, 38.5 and 36.5 per cent, respectively, for adolescent boys aged from 14 to 19 and girls aged from 14 to 17. This higher concentration of hemoglobin in adolescent persons, corresponding to a saturation index of 1.1 if calculated on the basis of standards for adults, has not hitherto been reported.

The availability of accurate standards for hemoglobin and volume coefficients for children should make possible a more accurate diagnosis of anemia in children, as it has in adults.[14] In adults high volume and color indexes are the most conclusive evidence available that a patient has pernicious anemia or a related anemia which will respond to liver therapy, and low saturation, color and volume indexes, the best evidence that anemia is due to relative deficiency in iron (in cases of chronic hemorrhage) or to absolute (nutritional) deficiency and that the condition will respond to large doses of iron.

The average values for the erythrocyte count, hemoglobin content, hemoglobin coefficient, cell volume, volume coefficient and color, volume and saturation indexes agree well with those previously reported [4b] for a smaller series of similar subjects and with the averages obtained by other workers in this field (tables 1 and 2).

The percentages of reticulocytes (chart 3) are the same, averaging 1.5 (1.46), with a range of from 0.5 to 3, for persons of the two sexes and all the ages included in this study. It bears no relationship to the total erythrocyte count, a fact which was not anticipated. The absolute number of reticulocytes, therefore, follows the total red cell count closely and is of little or no diagnostic value. It is recommended that reticulocyte counts be reported in percentages only. It should be noted that with the technic [4b] used the average counts are much higher than those usually reported. When this technic is used a count of less than 0.3 per cent is a definite indication of hypofunction of the marrow, and a count of more than 4 per cent, of hyperfunction.

14. Haden, R. L.: Accurate Criteria for Differentiating Anemias, Arch. Int. Med. **31**:766 (May) 1923. Osgood, E. E.; Haskins, H. D., and Trotman, F. E.: The Value of Accurately Determined Color, Volume and Saturation Indexes in Anemias, J. Lab. & Clin. Med. **17**:859 (June) 1932. Osgood, E. E., and Haskins, H. D.: Causes, Classification and Differential Diagnosis of Anemias, Ann. Int. Med. **5**:1367 (May) 1932.

The total and differential leukocyte counts show no significant differences between the sexes at any age but display definite variations for the different age groups. The white cell count (chart 4) is higher for children aged from 4 to 7, with an average of 10,400 (10,365) and a range of from 6,000 to 15,000 per cubic millimeter, than it is for boys and girls from 8 to 18, with an average of 8,300 (8,342) and a range of from 4,500 to 13,500, or for adults, with an average of 7,400 (7,447) and a range of from 4,500 to 11,500. It should be noted that the range necessary to include 95 per cent of the values for adults is definitely wider than that usually given, 2 per cent of the results being less or greater than from 5,000 to 10,000 cells per cubic millimeter.

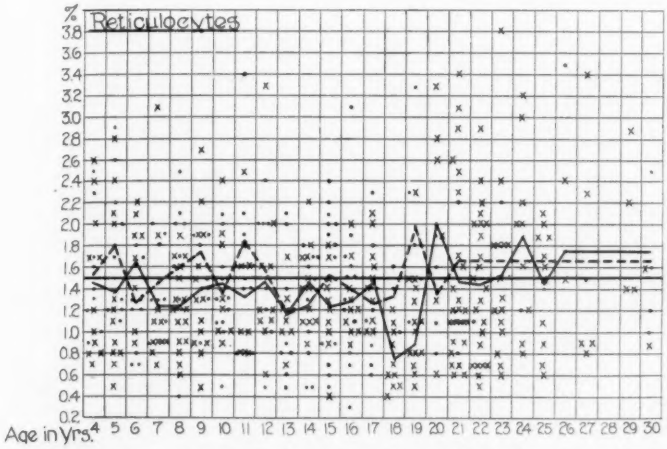

Chart 3.—Curves for the average values and the distribution of individual values for reticulocytes, expressed in percentages, for 275 males and for 173 females.

The number of segmented neutrophils (chart 4) is definitely lower for persons of all ages than the values usually given and shows a wider variation. Children aged from 4 to 14 have a lower average percentage, 38 (37.6), with a range of from 18 to 58 per cent, than adolescent boys and girls aged from 15 to 19 with an average of 48 (47.65) per cent and a range of from 25 to 75 per cent, or than adults, with an average of 54 (54.26) per cent and a range of from 33 to 78 per cent. This confirms a long held impression that the values usually given in textbooks are too high.

The separation of the staff cells (table 2) from the segmented neutrophils is not sufficient to explain the discrepancy, nor is the inclusion of disintegrating cells in the count, as the greatest value for the average total neutrophil count for adults that could be obtained by combining these results would be 58.5 per cent. It is of interest that

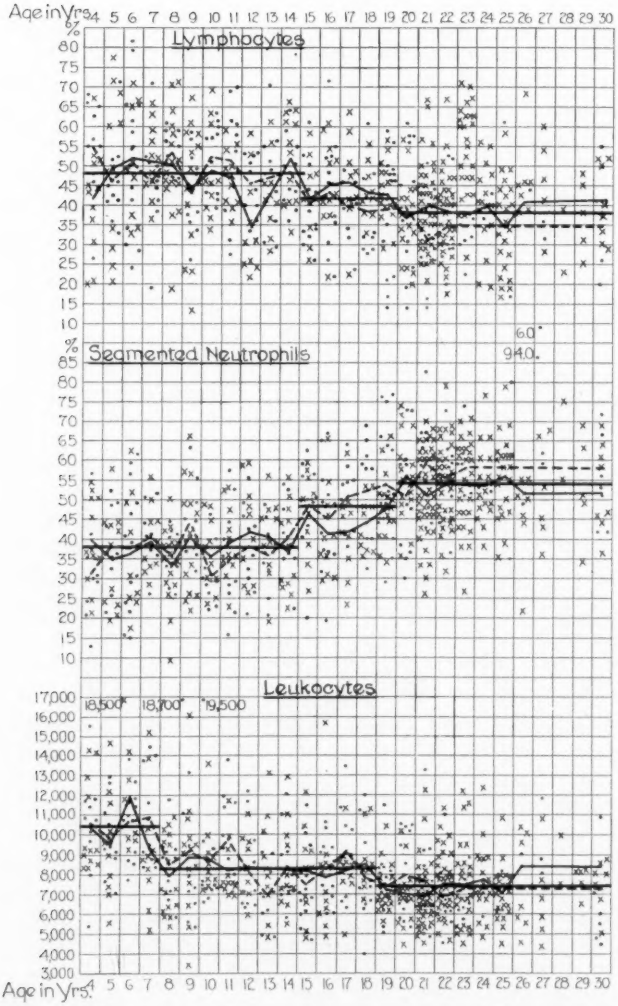

Chart 4.—Curves for the average values and the distribution of individual values for lymphocytes, segmented neutrophils and the total number of leukocytes for 365 males and 232 females. The values for the lymphocytes and segmented neutrophils are expressed in percentages; those for the total number of leukocytes, in thousands.

The number of staff cells is higher for children aged from 4 to 13, with an average of 3 (3.07) per cent and a range of from zero to 10 per cent, than for adults, with an average of 0.8 (0.78 per cent) and a range of from zero to 5 per cent.

The number of lymphocytes (chart 4), as might be expected, is in inverse ratio to that of the neutrophils but is much higher than the

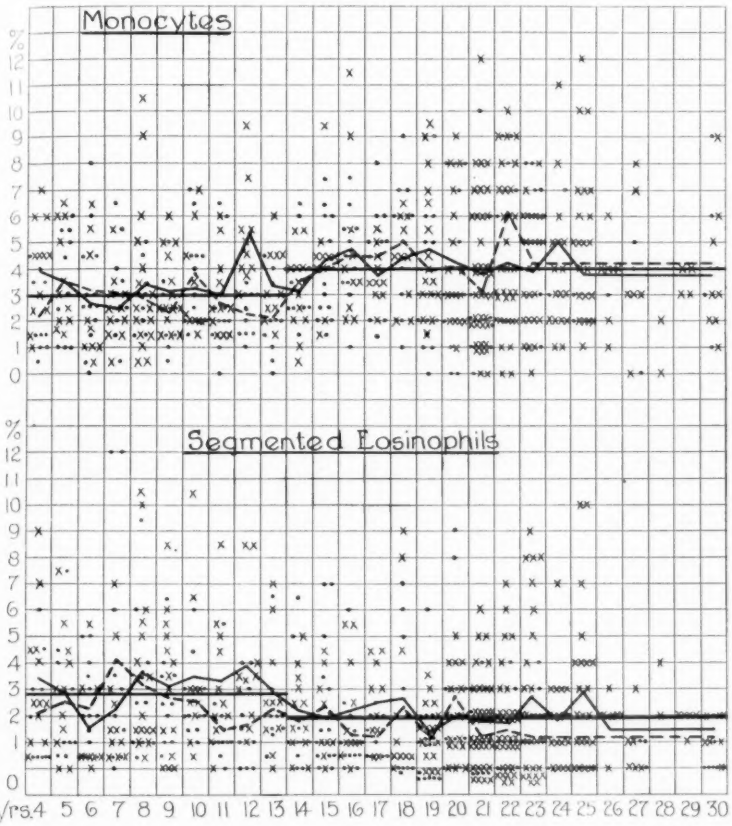

Chart 5.—Curves for the average values and the distribution of individual values for monocytes and segmented eosinophils, expressed in percentages, for 365 males and 232 females.

value usually employed. Children aged from 4 to 14 have an average count of 48 (48.21) per cent, with a range of from 21 to 71 per cent, and adolescent boys and girls from 15 to 19, an average of 42 (41.91) per cent and a range of from 22 to 62 per cent, while adults have an average of 38 (37.76) per cent and a range of from 18 to 65 per cent.

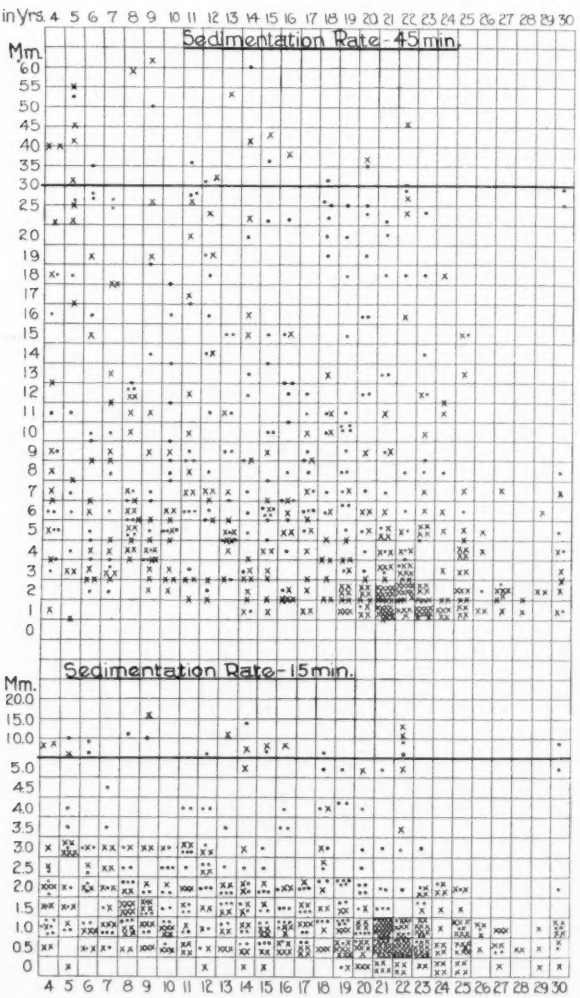

Chart 6.—Distribution of the individual values for the sedimentation rate, obtained for 340 males and 218 females at the end of forty-five minutes and of fifteen minutes, expressed in millimeters.

The number of monocytes and of eosinophils (chart 5) shows an inverse relationship, the percentage of monocytes being higher for adults and that of eosinophils higher for children. The number of monocytes averages 3 (3.08) per cent and ranges from 0.5 to 7 per cent for children aged from 4 to 13; for persons past the age of 14 the average is 4 (4.18) per cent and the range from 0 to 9 per cent. The number of segmented eosinophils averages 2.8 (2.79) per cent for children, with a range of from 0 to 8 per cent, and for persons past the age of 13 the number decreases to an average of 1.9 (1.9) per cent with a range of from zero to 6 per cent.

The number of basophils (table 2) shows no variation with age or sex, the average being 0.5 (0.52) per cent and the range from 0 to 2 per cent.

Disintegrating cells are often omitted in differential counts, but this introduces an error in the percentage of all the other cell types. The number of disintegrating cells furnishes an index of the rate of cell destruction. The increase in the number of disintegrating cells in cases of leukemia is often of diagnostic aid. These cells are more numerous in children, averaging 5 (4.89) per cent, with a range of from 0 to 10 per cent, than in adults, for whom the average is 3.5 (3.47) per cent and the range from 0 to 7 per cent.

In addition to the cell types listed in the table, Türk cells, plasma cells and eosinophil staff cells were found with sufficient frequency to justify one's regarding them as normal cells of the blood. An occasional promyelocyte or a large lymphocyte was found.

The sedimentation rates (chart 6) show a range of from 0 to 5 mm. in fifteen minutes and from 1 to 30 mm. in forty-five minutes. Undoubtedly, some high sedimentation rates are due to mild infections, such as chronic sinusitis or infected teeth, which are difficult to exclude by a routine physical examination. It is probable that the rate of 15 mm. in forty-five minutes, which includes 80 per cent of the results, is the upper limit of normal for persons entirely free from infection.

SUMMARY

Studies of the erythrocyte count, hemoglobin content, hemoglobin coefficient, cell volume, volume coefficient, color, volume and saturation indexes, reticulocyte count, total and differential leukocyte counts and sedimentation rate for more than 500 persons representing both sexes and all ages from 4 to over 30 years are presented.

The results of these studies are summarized in charts 1 to 6 and in table 2.

The normal hematologic standards given in table 2 should be used as a basis for interpretation until they are superseded by more extensive data of equal or greater accuracy.

RÔLE OF PRESSOR SUBSTANCES IN ARTERIAL HYPERTENSION

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In the past, several investigators have postulated increased amounts of hormones of a pressor nature in the blood of patients with arterial hypertension. Others have suggested as a cause of hypertension the retention in the blood and tissues of metabolic products having a pressor action. One of us (Dr. Weiss [1]) has recently discussed these various theories, and a critical analysis with references can be found in that paper. In recent years, interest in the relation of such substances to hypertension has been stimulated again, largely through the work of two groups of investigators in Germany. Lange and Felix,[2] in 1933, claimed to have found diminished amounts of a specific depressor substance in the blood and increased amounts in the urine of patients suffering from essential hypertension, and increased amounts in the blood and decreased amounts in the urine of patients with nephritic hypertension. They advanced the theory that essential hypertension is accompanied by a lowering of the renal threshold for this specific depressor substance, thus producing a lower concentration in the blood and thereby allowing the constrictor mechanism to overact. Because of the well recognized difficulties in isolating the various depressor materials present in blood and other tissues, and because of the complicated methods necessary for quantitative studies, the interpretation of these findings is difficult.

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1. Weiss, Soma: The Etiology of Arterial Hypertension, Ann. Int. Med. **8**: 296, 1934.

2. Lange, Fritz: Der stoffliche Anteil an der Regulation des Kreislaufes und seine Bedeutung für die Hypertonie, Klin. Wchnschr. **12**:173, 1933. Felix, K.: Zur Chemie der stofflichen Kreislaufregulation, ibid. **12**:176, 1933.

In a series of studies Bohn and his associates,[3] working in Volhard's Clinic, found markedly increased amounts of pressor material in both the blood and the urine of patients with "pale" hypertension (malignant and nephritic types) and noted its absence or its presence in only small amounts in normal subjects and in patients with "red" hypertension (essential and arteriosclerotic types). They claimed that by determining the amounts of pressor material in extracts of either the blood or the urine of hypertensive patients they could differentiate the pale from the red type. They thus confirmed Volhard's original postulation that pale hypertension is caused by increased amounts of circulating constrictor substances in the blood whereas red hypertension is the result of nervous and mechanical factors. Their methods of preparing extracts from the blood and urine are relatively simple, and their results appear to be clearcut and rather striking. The investigations of Marx and Hefke,[4] based on a slightly different technic, were confirmatory of these findings. Anselmino and Hoffmann,[5] using a method of dialysis, also separated active vasopressor material from blood. De Wesselow and Griffiths[6] in England, and Page[7] in this country, on the other hand, failed to confirm Bohn's findings with blood extracts. De Wesselow and Griffiths, using Bohn's methods, were unable to find any pressor material in the blood. Page found a pressor material in the blood; however, it was present as often in normal as in hypertensive subjects. Because of the importance of these findings in relation to the etiology and mechanism of hypertension, we have investigated certain aspects of this problem.

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3. Bohn, H.: Untersuchungen zum Mechanismus des blassen Hochdrucks: I. Mitteilung. Gefässverengernde Stoffe im Blute beim blassen Hochdruck, Ztschr. f. klin. Med. **119**:100, 1931; Zum Mechanismus des blassen Hochdrucks, vasoaktive und antidiuretische Stoffe im Blut, Liquor und Harn, Kreatin und Kreatinin im Blut und Harn, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **45**:182, 1933. Bohn, H., and Hahn, F.: Untersuchungen zum Mechanismus des blassen Hochdrucks: VI. Blutdrucksteigernde Stoffe im Harn, insbesondere beim blassen und roten Hochdruck, Ztschr. f. klin. Med. **123**:558, 1933.

4. Marx, H., and Hefke, K.: Untersuchungen zur Pathogenese der Hypertonie, Klin. Wchnschr. **12**:1318, 1933.

5. Anselmino, K. J., and Hoffmann, F.: Nachweis der antidiuretischen Komponente des Hypophysenhinterlappenhormons und einer blutdrucksteigernden Substanz in Blute bei Nephropathie und Eklampsie der Schwangeren, Klin. Wchnschr. **10**:1438, 1931.

6. de Wesselow, O. L. V. S., and Griffiths, W. J.: On the Question of Pressor Bodies in the Blood of Hypertensive Subjects, Brit. J. Exper. Path. **15**: 45, 1934.

7. Page, I. H.: Personal communication to the authors, J. Exper. Med. **61**: 67, 1935.

PLAN OF INVESTIGATION

The purpose of this investigation was to test the urine and blood of all types of hypertensive patients as well as of normal subjects for pressor substances by means of Bohn's technic. Our work has consisted chiefly in studies of urine extracts because in preliminary experiments we obtained no significant pressor effect from blood extracts prepared by various methods; furthermore, large quantities of urine could easily be obtained, and the substances to be studied could be more highly concentrated. We have limited ourselves to repeated observations on a small group of selected patients as it was felt that this would give the most significant information.

Extracts were prepared from the urine of each of twenty-five subjects, including seven with malignant hypertension, four with chronic nephritis and hypertension, six with essential hypertension and eight normal subjects.

The criteria adopted for the diagnosis of malignant hypertension included a marked elevation of both systolic and diastolic blood pressures, definite eyeground changes, such as hemorrhages, exudate and papilledema, and a relatively short duration of symptoms. The patients with essential hypertension showed only slight renal damage and had no retinal disturbances except for arteriosclerotic changes. Table 1 briefly summarizes these findings.

METHODS

In the preparation of the urine extracts Bohn's technic was followed in its original form as well as with modifications. Twenty-four hour amounts of urine were collected on ice, and the pressor material was adsorbed on a specially activated charcoal by shaking mechanically for five hours. The amount of charcoal used varied between 4 and 8 Gm. per liter of urine, depending on the amount of albumin present. The charcoal was then filtered off by suction and the dried charcoal extracted in a Soxhlet apparatus, first with acetone and finally with 95 per cent alcohol. In each case the extraction time was three hours. The extracts were evaporated to dryness in vacuo at temperatures not exceeding 37 C., and the residue of each extract was suspended or dissolved in 15 cc. of physiologic solution of sodium chloride. The extracts were then stored on ice until used.

Modifications of this technic resulted in no appreciable increase in pressor material. Since the alcohol extract was of necessity kept at a temperature of from 80 to 90 C. during extraction, cold extraction by continuous shaking for many hours was performed as an alternative method. Alcohol and acetone extraction of the charcoal in this way considerably diminished the activity of the extracts; prolonged extraction in the Soxhlet apparatus with both acetone and alcohol did not appreciably increase their activity.

In the preparation of blood extracts two technics were used: Fourteen of the blood extracts were prepared by Bohn's technic, which consisted in adding from 40 to 50 cc. of fresh blood to three times this volume of 95 per cent alcohol. The mixture was shaken and allowed to stand in the icebox for five hours. The precipitate was filtered off, and the filtrate was added to three times the original

blood volume of absolute alcohol and refiltered. The filtrate was then evaporated almost to dryness in vacuo and the residue dissolved or suspended in a volume of physiologic solution of sodium chloride equal to one half of the original volume of blood. The final extract was kept on ice until used.

In the preparation of five of the extracts Page's [7] modification of Bohn's method was used. Freshly drawn citrated blood was centrifugated and the plasma pipetted into nine times its volume of absolute alcohol. The procedure to this point was completed within ten minutes after the venipuncture. The resulting mixture was allowed to stand on ice over night and was then rapidly filtered at a temperature not over 4 C. This removed the protein and most of the lipoid material.

TABLE 1.—*Summary of Diagnoses and Clinical Findings in Patients Studied*

Case	Patient	Diagnosis	Age	Sex	Average Blood Pressure, Mm. Hg	Nonprotein Nitrogen, Mg. per 100 Cc.	Renal Function	Fundi	Duration of Symptoms
1	R. S.	Malignant hypertension	46	M	200/140	36	Normal	Choking of disks; hemorrhages; narrowing of vessels	9 mos.
2	B. S.	Malignant hypertension	43	M	230/140	39	Slightly diminished	Choked disks; exudate; hemorrhages	8 mos.
3	E. H.	Malignant hypertension	29	M	220/140	32	Normal	Narrowing of vessels; hemorrhages	3 yrs.
4	R. B.	Malignant hypertension	37	M	190/135	26	Normal	Narrowing of vessels; hemorrhages	2 wks.
5	S. L.	Chronic nephritis	41	M	260/150	44	Diminished	Choked disks; hemorrhages	2½ yrs.
6	P. S.	Malignant hypertension	56	M	230/155	32	Diminished	Choked disks; hemorrhages	1 yr.
7	B. D.	Chronic nephritis	52	F	240/130	44	Diminished	Hemorrhage; exudate	2 yrs.
8	C. C.	Chronic nephritis	21	M	175/124	49	Diminished	Narrowing of vessels	4 yrs.
9	J. A.	Malignant hypertension	49	F	240/130	32	Normal	Hemorrhage; exudate	1 yr.
10	M. K.	Chronic nephritis	37	F	190/122	37	Diminished	Narrowing of vessels	2 yrs.
11	W. H.	Malignant hypertension	47	M	240/160	38	Slightly diminished	Hemorrhage; exudate	6 mos.
12	J. L.	Essential hypertension	61	M	170/ 80	25	Slightly diminished	Arteriosclerotic retinitis	2 yrs.
13	R. C.	Essential hypertension	33	M	190/134	45	Normal	Narrowing of vessels	1 yr.
14	M. B.	Essential hypertension	39	F	220/110	36	Normal	Slight narrowing of vessels	1 yr.
15	A. T.	Essential hypertension	62	F	190/110	34	Normal	Nicking of veins	2 yrs.
16	J. W.	Essential hypertension	48	M	176/108	32	Normal	Normal	1 yr.
17	J. M.	Essential hypertension	64	M	170/ 90	32	Normal	Nicking of veins	1 yr.

Evaporation in vacuo to one half of the original volume of the plasma was carried out on the filtrate. The extract was then chilled to below 4 C. and any remaining lipoid material precipitated and removed. The filtrate was kept on ice until injected.

About seventy cats were used in the studies with these extracts. Although sodium amytal (sodium salt of iso-amyl-ethyl barbituric acid) proved to be a satisfactory anesthetic, dial with ethyl carbamate (urethane) [8] appeared to have

8. Dial with ethyl carbamate (urethane) is a solution prepared by the Ciba Company, Inc., 1 cc. containing diallylmalonylurea 0.1 Gm., ethyl carbamate (urethane) 0.4 Gm., mono-ethylurea, amount not stated, and distilled water.

a less depressant effect on the animals' vasomotor responses and was therefore used in the majority of the experiments. Both anesthetics were given intraperitoneally; the dose of sodium amytal was 0.05 Gm. per kilogram of body weight and that of the dial solution 0.7 cc. per kilogram of body weight. Ether, chloral and ethyl carbamate (urethane) were tried as anesthetics but did not prove as satisfactory as sodium amytal and dial.

The animals were regularly prepared by exposing both common carotid arteries and both vagus nerves and inserting a cannula into the trachea. The blood pressure was obtained from the femoral artery by means of a mercury manometer and was recorded on a smoked drum. Sodium citrate did not prove satisfactory as an anticoagulant; the wide variations in the blood pressure produced by the extracts caused the infusion of enough citrate into the blood stream to diminish the animals' pressor responses to a considerable degree. This was true even when concentrations as low as 5 per cent were used. Therefore, in most experiments a 0.5 per cent aqueous solution of heparin was employed. The arterial cannula, with a capacity of 5 cc., was filled with the heparin solution and the remainder of the system with isotonic sodium chloride. This method proved very satisfactory in preventing the formation of clots, and required only small amounts of heparin.

Urine extract was injected at a uniform rate into the femoral vein and washed into the circulation with 3 cc. of warm physiologic solution of sodium chloride. In order to standardize our results, 3 cc. of the extract, representing one fifth of the original twenty-four hour volume of urine, was used for each injection. A similar standard procedure was employed for the injection of blood extract. By testing a single extract on several animals, any variation in the pressor response between these animals was brought out and a true evaluation of the potency of a given extract could be made. Spontaneous variations in the response of each cat were likewise noted by frequent injections of the extract being tested.

The carotid sinus "pressor" reflex was elicited frequently by occlusion of both common carotid arteries in order to compare its effect with that of the extract and also in an attempt to test the animal's vasomotor sensitivity. Epinephrine in doses of 1 cc. of a 1:100,000 solution was used for similar purposes. In all cases the injection of extracts was preceded by the injection of a similar volume of saline solution in order to determine the blood pressure effect due to blood volume changes alone.

RESULTS

Types of Blood Pressure Responses Obtained.—The typical blood pressure response produced by the injection of urine extract consisted essentially in first a depressor and then a pressor effect. The depressor portion of the curve lasted from ten to thirty seconds and the pressor portion from three to thirty minutes. The magnitude of these two effects varied considerably in different experiments. A pure depressor curve was frequently obtained; a pure pressor curve more rarely. These various blood pressure reactions are similar to those described by Bohn and suggest, therefore, that we are dealing with the same pressor substance in the urine that he studied. Chart 1 shows the types of blood pressure curves observed by us.

Relationship of Pressor Substance to Hypertension.—Our results are summarized in table 2. We found no relationship between the magnitude of the pressor effect and hypertension of any type. In fact, we obtained on the whole more marked pressor responses with extracts of urines from normal subjects than with those of urines from patients having malignant and nephritic hypertension. The pressor effect was present to some degree, however, in about the same percentage of all groups of patients studied. We were unable to confirm Bohn's statement that pure pressor curves were obtained only in pale hypertension; in fact, all our pure pressor curves were obtained with extracts from the urines of normal patients.

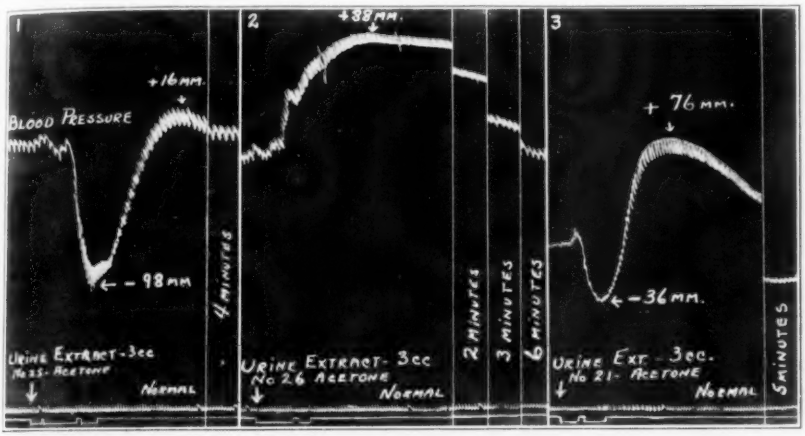

Chart 1.—Tracings obtained when extracts of urines from normal subjects were used, representing the various types of reactions obtained from all types of patients. These tracings correspond to Bohn's curve types 1, 3 and 2, respectively. Note that the pure pressor curve was obtained from a normal subject.

The factors influencing the type of blood pressure curve obtained with the urine extract of a given patient divide themselves into: variations related to the preparation and age of the extract, variations in the response of the test animal and daily variations in the excretion of the pressor material.

Variations in the Extract.—In his studies Bohn assumed that the acetone fraction removed only depressor material from the urine, and for this reason he tested only the alcohol fraction. We varied the time of extraction with acetone from a few minutes to twenty-four hours but were unable to substantiate Bohn's claim, and consequently have

tested both the acetone and the alcohol fraction from each urine studied. We have found no evidence that acetone selectively removes the depressor substances. In fact, on extracting with acetone for the same length of time as with alcohol, the acetone fraction produced in most cases more marked pressor and no greater depressor effect than did the alcohol fraction. By reversing the extraction process it was found that when the charcoal was extracted first with alcohol all the depressor and only half the pressor material was present in the alcohol, while 50 per cent of the pressor material remained to be extracted finally by the acetone. In the control experiment on the same sample of urine the acetone fraction contained all the pressor material and the final alcohol fraction only depressor material. This clearly demonstrates that under the conditions of our experiments, and in contradistinction to Bohn's findings, acetone is a better extractive for the pressor material than is alcohol.

TABLE 2.—*Summary of Pressor Responses Obtained from Extracts of Urines*

Condition of Patients from Whose Urines Extracts Were Obtained	Patients	Number Whose Urine Extracts Yielded Given Maximum Pressor Effect, Mm. Hg.					Urine Extracts Tested	Injections of Extracts
		0-24	25-49	50-74	75-99	100+		
Normal	8	1	1	4	0	2	18	99
Essential hypertension	6	3	2	0	0	1	8	30
Malignant hypertension	7	1	1	4	1	0	19	131
Chronic nephritis	4	1	1	2	0	0	8	39
Total	25	6	5	10	1	3	53	299

The age of the extracts after preparation, when these were kept in the icebox, appeared to have no influence on the type of response they produced in the cats. This was true for at least four weeks; in some cases the pressor effects then disappeared.

Variable Factors in the Cat.—The degree of both pressor and depressor responses in the same animal from repeated uniform doses of a single extract varied markedly for no discernible reason. Thus, in an experiment lasting several hours, an originally good pressor response was sometimes observed to disappear and then to reappear later, on successive test injections. This occurred in spite of attention to such details as the rate of injection, the temperature of the injected material and the temperature of the animal. The possibility that a prolonged action of the injected substance might account for variations in results was eliminated by always waiting at least ten minutes, or until the blood pressure had returned to its preinjection level, before testing another extract. A comparison of curves 4-A and 4-B in chart 2 demonstrates this change in the blood pressure response during a single experiment.

Bohn has stated that the initial blood pressure of the animal influences the pressor response to urine extract and that if it is too high it should be lowered by atropine, bleeding or the use of secondary butyl beta bromallyl barbituric acid sodium salts. We were unable to increase the pressor response of test animals to the urine extract by artificially lowering the blood pressure, either through the use of deeper anesthesia with dial, sodium amytal, chloral or ether, or through the use of atropine, bleeding or drugs having a depressor effect, such as amylnitrite or acetylcholine. Although increased pressor effects were occasionally obtained by lowering the blood pressure through bleeding, this increase

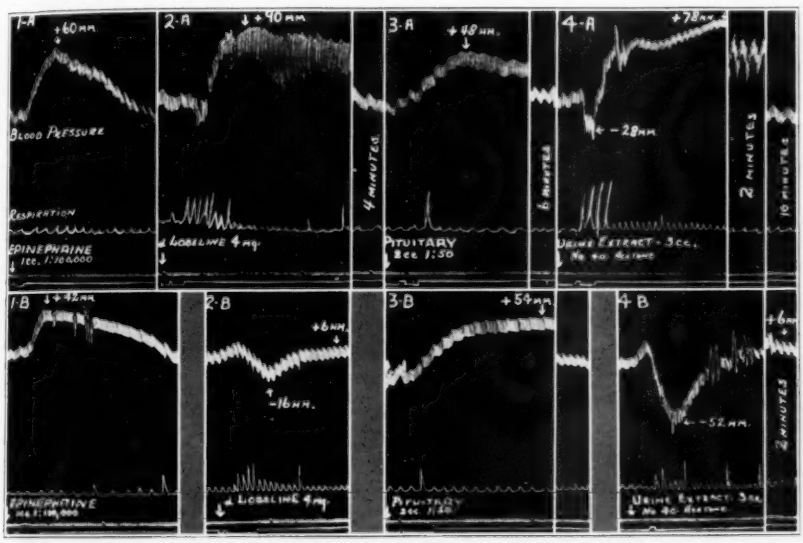

Chart 2.—The top row represents the blood pressure and respiratory response to the consecutive injection of epinephrine, alpha-lobeline, pituitary, and an extract of urine from a normal subject. The bottom row represents the response to these substances during a period when the pressor response to the urine extract had spontaneously disappeared. Note the similarity of the curve produced by lobeline to that produced by the urine extract during periods of both maximal and minimal response. Note also the lack of relationship between the pressor responses to epinephrine and pituitary and the response to the extract. This experiment also demonstrates the spontaneous change in the response of a test animal to a urine extract, which has been frequently encountered by us.

was proved to be largely due to the change in blood volume, as a rise in blood pressure approaching the difference of the pressor effects obtained could be produced by the injection of an equal volume of saline

solution. Increased pressor effects were, however, occasionally observed following spontaneous changes of the blood pressure to a lower level.

Comparison of the action of urine extracts from different patients would be greatly simplified if there existed a method for measuring the sensitivity of the test animal to the extract at a given time. Bohn thought that this sensitivity somewhat paralleled the action of epinephrine, and Page found a close relationship between the pressor effect of blood extracts and the carotid sinus pressor reflex. We have carried out both procedures, together with injection of the extracts, as a routine but have found no relationship whatsoever. In many cases the full pressor effect of epinephrine remained after that of the urine extract had disappeared (chart 2); furthermore, the epinephrine effect occasionally showed complete reversal during periods when maximal pressor effects were obtained from the extracts. Likewise, the pressor effect of the extract was found to be maximal during periods when the carotid sinus pressor reflex had disappeared. Both bilateral section of the vagus nerves and complete atropinization (1 mg. per kilogram of body weight) were carried out in some experiments, but neither of these procedures increased the pressor responses nor did they prevent the spontaneous variations in response to the extracts.

A comparison of the reactions of different animals to the same extract showed a satisfactory uniformity when the extract was injected under similar conditions.

Daily Variations in Excretion of Pressor Substance.—Extracts of the urine from a given patient, collected from day to day, generally gave the same type of blood pressure curve; however, marked variation in the daily excretion of the pressor substance was occasionally noted. This variation did not seem to be directly related to the volume of urine excreted; in fact, highly colored urines of small volumes appeared to produce the greatest pressor effects.

Nature of Pressor Substance Found in Urine.—Although the pressor material found in the urine bore no relationship to hypertension, its presence in such a large percentage of the urines tested led us to attempt to determine its nature and mode of action.

A depressor effect preceded the pressor curve in a large percentage of cases and suggested the possibility that the pressor portion of the curve was a nonspecific overcompensation on the part of the test animal to the initial depression of the blood pressure. This assumption was disproved by the fact that at times pure pressor effects were obtained and also by the fact that atropine abolished the initial depressor effect without materially changing the pressor response. The fact that atropine abolishes the depressor effect suggests that the depressor substances are in part choline or its derivatives.

Bohn and others have suggested that the pressor effect obtained from the urine is probably due to the presence of pituitary.[9] We compared the response of the test animals to the urine extracts with the response to pituitary [10] but found no relationship to exist between them. The pressor response to pituitary remained at a constant level or was even increased at times when the animal's response to the extract had entirely disappeared (chart 2). The dissimilarity of action between pituitary and the urinary pressor substance was brought out more conclusively in experiments which showed that the activity of pituitary is completely abolished by our method of extraction. In these experiments 4 cc. of pituitary was added to one half of a twenty-four hour specimen of urine and the remainder of the urine used as a control; both urine samples were carried through the usual method of extraction and concentrated so that 3 cc. of the final extract represented one fifth of a twenty-four hour volume of urine. Urines having a good pressor effect and others having only a depressor effect were extracted in this manner. In no case was there any difference between the blood pressure effect of the controls and that of the urine to which pituitary had been added. Had the pituitary remained active or been extracted, the 3 cc. of extract injected should have contained forty times the amount of pituitary necessary to raise the blood pressure of the animal 50 to 80 mm. of mercury. Likewise, repeated injections of epinephrine carried out in most experiments have demonstrated that there is no relationship between its action and that of the urine extract (chart 2). These observations clearly indicate that neither epinephrine nor pituitary is the pressor substance present in the urine. The shape of the pressor curves obtained from the urine extract, on the other hand, resembled in many respects those obtained from drugs with central vasomotor action. We have therefore compared the animal's response to the urine extract with that to alpha-lobeline. This substance has a central action and has been studied by Norris and Weiss [11] and others.[12]

9. Coester, C.: Untersuchungen zum Mechanismus des blassen Hochdrucks: IX. Pressorische und antidiuretische Stoffe im Harn beim blassen Hochdruck, Ztschr. f. klin. Med. **126**:593, 1934. Bohn.[3b] Anselmino and Hoffmann.[5]

10. A double strength surgical pituitary.

11. Norris, V. H., and Weiss, S.: The Pharmacological and Therapeutic Properties of Alpha-Lobelin: A Comparison of Its Action on the Respiratory Center with That of Other Respiratory Stimulants, J. Pharmacol. & Exper. Therap. **31**:43, 1927.

12. Wieland, H.: Ueber die Alkaloide in Lobeliapflanzen, Ber. d. deutsch. chem. Gesellsch. **54**:1784, 1921. Edmunds, C. W.: On the Action of Lobelin, Am. J. Physiol. **11**:79, 1904.

The pressor action of alpha-lobeline was found to parallel closely the action of the extract; in fact, in experiments in which the two were injected repeatedly during changes in sensitivity of the cat, the pressor actions not only paralleled each other but the blood pressure curves showed strikingly similar changes in such details as the initial depressor effect, and delays in the pressor effect when the cat's sensitivity was rapidly diminishing.

Since the action of the urinary pressor substance closely parallels that of alpha-lobeline (a substance acting on the central nervous system) and shows no relationship to epinephrine and pituitary (substances having a peripheral action) it is suggested that the rise in blood pressure is due to central rather than to peripheral action. A comparison of the action of the extract with those drugs is shown in chart 2. In this experiment epinephrine, pituitary, lobeline and a single urine extract were repeatedly injected. It is seen that when the test animal had lost its pressor response to the extract the pressor action of lobeline likewise diminished, but that of epinephrine and of pituitary continued without change.

Although we have not compared the action of sympathin with that of the urinary pressor extract, it is obvious that the actions of the two substances are very dissimilar. The several types of sympathin are fairly unstable substances and have only a peripheral action [13] whereas the pressor material is very stable and has a central action.

Effect of Blood Extracts.—In seventeen cases the method of Bohn, and in five cases the method of Page, was followed in extracting the blood. Extracts from the blood of both normal subjects and patients with malignant, essential and nephritic hypertension failed to produce any pressor effect other than that expected from the amount of fluid injected into the test animal.

COMMENT

In this study we have had some difficulty in reaching definite conclusions because of the many variable factors encountered. The determination of the pressor effect of a given extract required several observations on two or more test animals, and the injections had to be made at corresponding periods in each experiment. Also, the pressor effects from both the acetone and the alcohol fraction had to be considered together in estimating the total effect of a single extract.

The response of the test animal to a volume of saline solution equal in amount to that used in injection of the extracts was quite marked

13. Cannon, W. B.: Chemical Mediators of Autonomic Nerve Impulses, Science **78**:43, 1933.

at times and had to be determined before estimating the pressor effects of the extracts. The types of pressor effects obtained from saline solution alone are shown in chart 3; elevations of the blood pressure as high as 30 mm. of mercury were frequently seen. In addition, numerous other factors previously mentioned had to be considered before the amount of pressor action of any extract could be estimated.

Because of the necessity of controlling these many variables, we feel that great caution should be used in arriving at significant conclusions in this type of problem. The failure to control properly such factors, in our opinion, is largely responsible for the conflicting results reported by various investigators concerning the relation of pressor substance to hypertension.

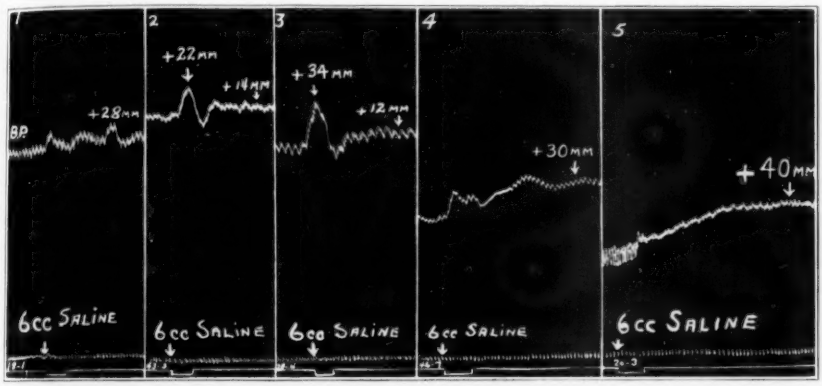

Chart 3.—Curves representing the pressor effects obtained from physiologic solution of sodium chloride. Curves 1, 2 and 3 are the types usually encountered, but elevations of from 30 to 40 mm. were frequently seen.

SUMMARY AND CONCLUSIONS

1. The pressor substance or substances in the urine of patients with hypertension of any type is not increased above the normal. The blood pressure response of test animals to extracts of urines from normal and hypertensive patients was essentially the same.

2. Removal of the depressor substances from the urine by acetone extraction did not prove satisfactory; on the whole, the acetone fraction contained more pressor material and less depressor material than did the alcohol fraction.

3. Although the exact nature of the pressor substance found in urine was not determined, we have presented experimental evidence

indicating that it is not epinephrine or pituitary, and that it is a rather stable water-soluble substance that acts centrally rather than on the peripheral nerve endings or on the vascular system.

4. The difference in the pressor effect of extracts from different patients, unless great, is not significant, because the methods of extracting and testing the pressor material are not sufficiently accurate.

THE RENAL THRESHOLD FOR DEXTROSE IN MAN

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By the renal threshold for dextrose is generally understood that concentration of sugar in the blood above which sugar appears in the urine. In man this phenomenon has long been of interest, especially in relation to diabetes. It has been frequently studied, but current opinion [1] is not in agreement as to the concept comprised in the term threshold for dextrose. The view of a fixed, unalterable concentration of dextrose in the plasma above which dextrose uniformly appears in the urine seems to be untenable. It is certain that by the ordinary methods of measurement there are many factors which cause the concentration to vary and that it not only is different in various persons but is not characteristic for a single subject. It is the purpose of the investigation reported here to examine some of the factors which it seemed might be largely responsible for a possibly apparent inconstancy of the renal threshold for dextrose.

THEORETICAL CONSIDERATIONS

In the light of our present knowledge of renal function as derived from direct experiments on the amphibian kidney [2] and the implications which they allow us to draw as to the mode of excretion of the urinary constituents by the mammalian kidney [3] and even by the human kidney,[4]

From the Scripps Metabolic Clinic.

1. Himsworth, H. P.: The Relation of Glycosuria to Glycaemia and the Determination of the Renal Threshold for Glucose, Biochem. J. **25**:1128, 1931. Campbell, R. A.; Osgood, E. E., and Haskins, H. D.: Normal Renal-Threshold for Dextrose, Arch. Int. Med. **50**:952 (Dec.) 1932.

2. Richards, A. N.: Methods and Results of Direct Investigation of the Function of the Kidney, Baltimore, Williams & Wilkins Company, 1931. Oliver, J., and Shevky, E.: A Comparison of the Manner of Excretion of Neutral Red and Phenol Red by the Frog's Kidney, J. Exper. Med. **50**:15, 1929; A Mechanism of Conservation in the Kidneys of the Winter Frog, ibid. **50**:601, 1929.

3. MacKay, E. M., and Oliver, J.: A Comparison of the Method of Excretion of Neutral Red and Phenol Red by the Mammalian Kidney, J. Exper. Med. **51**:161, 1930. Poulsson, L. T.: On the Mechanism of Sugar Elimination in Phlorrhizin Glycosuria, J. Physiol. **69**:411, 1930.

4. Chasis, H.; Jolliffe, N., and Smith, H. W.: The Action of Phlorhizin on the Excretion of Glucose, Xylose, Sucrose, Creatinine and Urea by Man, J. Clin. Investigation **12**:1083, 1933.

the normal retention of dextrose in the blood by the kidney seems in all probability to be brought about by the almost complete reabsorption by the tubules of dextrose which is filtered from the plasma in the glomerular filtrate. That this reabsorption is normally not absolutely complete is indicated by the work of Eagle [5] and of Van Slyke and Hawkins,[6] who by the use of very sensitive modern methods found measurable quantities of reducing substances in normal urine. However, this is such an insignificant amount at most that for practical purposes the urine may be considered free from sugar. It is known that when the concentration of blood sugar rises to high levels, above the so-called threshold for dextrose, gross quantities of dextrose appear in the urine. It is our belief that there is sufficient evidence to allow one to consider this threshold for dextrose as the concentration of dextrose in the plasma at which the reabsorption of dextrose by the renal tubules from the glomerular filtrate is insufficient to prevent the excretion of an appreciable quantity of dextrose in the urine. From the theoretical aspect, one of the factors which seems likely to be foremost in determining this concentration is the degree of renal activity—not alone the number of functioning renal units but the activity of these or the volume of glomerular filtrate being formed in each individual unit. If only a relatively few glomerulotubular units were active, it is reasonable to suppose that a much higher concentration of dextrose in the plasma would be required to cause sugar to appear in the urine than if the kidneys were fully active. On the other hand, with all of the renal elements functioning, diuresis might so reduce the reabsorption of dextrose that a concentration of dextrose in the plasma considerably lower than usual might be reached before sugar-free urine would be formed. A suggestion that this is probably the case came from experiments on the threshold for sodium chloride, which are to be presented elsewhere. When rabbits were put on a salt-free diet and copious diuresis was established, a chloride-free urine was obtained when the average concentration of chloride in the plasma was 500 mg. per hundred cubic centimeters of sodium chloride. If extreme diuresis was induced by the administration of large amounts of urea and water, the urine again contained chloride when the concentrations of chloride in the plasma were much lower, even as low as 230 mg. per hundred cubic centimeters in one case, shortly after which the animal succumbed. On this basis the threshold for dextrose was investigated in man under conditions of full and constant renal activity.

5. Eagle, H. S.: On the Nature of the Urine Sugars, J. Biol. Chem. **71**:481, 1927.

6. Van Slyke, D. D., and Hawkins, J. A.: J. Biol. Chem. **83**:51, 1929.

Various observers, beginning with Frank,[7] have noted that the renal threshold determined on the basis of a descending curve of sugar concentration in the blood may be entirely different from the threshold derived from an ascending curve. It is the usual conclusion [8] that the threshold level is much lower during a descending curve. The reason for this discrepancy probably rests in the dead space of the kidney and ureter. Hinsworth [1a] has considered the influence of this dead space, but not for the same reason. The urine from the bladder, as collected, has actually been formed from two to even sixty minutes before it reaches the bladder, depending on the rate of the secretion of urine—the lower the rate the greater the difference in time. With volumes of urine of 20 cc. or less per hour, the renal threshold determined on the basis of a descending curve of sugar concentration in the blood drawn at the middle of an apparent period of urine secretion would be much too low. The only way to remove this factor entirely would be to determine the renal threshold for dextrose during the continuous intravenous injection of dextrose, only those periods being selected in which the concentration of blood sugar during the fore-periods and after-periods was approximately the same. Obviously this method is impracticable for any series of observations. The error may be greatly reduced by insuring high volumes of urine and thus reducing the time interval represented by the urine in the dead space.

Many investigators are accustomed to thinking of the concentration of dextrose in the urine in determining the renal threshold. This figure is, however, determined not only by the excretion of dextrose but by the volume of urine. With a qualitative clinical test (Benedict's), such as is frequently made, a volume of urine of 30 cc. per hour will not give a positive reaction if it contains 200 mg. of sugar. With one-half this volume the same amount of sugar will give a strong reducing action. The only reasonable method of expressing the dextrose in the urine is in the rate of dextrose excreted per unit of time.[9]

The blood which forms the urine is arterial. There is quite a discrepancy between the concentration of dextrose in arterial blood and that in venous blood,[10] and the former is the one from which determinations of the level of the renal threshold for dextrose should be made. Technically, the difficulty of obtaining arterial blood may be overcome by the use of capillary blood, which is practically arterial so far as the sugar content is concerned.[10] The ideal condition would be to use

7. Frank: Arch. exper. Path. u. Pharmakol. **72**:387, 1913.

8. Goto, K., and Nobuzo, K.: Studies on Renal Threshold for Glucose, Arch. Int. Med. **27**:224 (Feb.) 1921.

9. Hawkins, J. A.; MacKay, E. M., and Van Slyke, D. D.: Glucose Excretion in Bright's Disease, J. Clin. Investigation **8**:107, 1929.

10. Foster, G. L.: Some Comparisons of Blood Sugar Concentrations in Venous Blood and in Finger Blood, J. Biol. Chem. **55**:291, 1923.

arterial plasma, but this is naturally not practicable. Then it is generally customary to use whole blood rather than plasma for analyses of blood sugar.

It must be remembered that not all of the reducing substances in either the urine or the blood are dextrose. In measuring the renal threshold for dextrose, only the fermentable reducing substances in both the blood and the urine should be determined. Otherwise, one must deal with a variable and unknown quantity of nondextrose reducing substances included in their figures for dextrose.

So far as possible, certain refinements have been introduced into the method of determining the threshold for dextrose which from the theoretical aspects discussed may determine the usual inconstancy of this figure.

EXPERIMENTAL PROCEDURE

Adequate volumes of urine and full renal activity were attained by the administration of urea and large quantities of water under conditions [11] which are known to yield this result. The patient was kept without food for twelve hours before and for the duration of the period of observation, so that the degree of renal activity might remain constant.[12]

Dextrose when given by mouth with a moderate quantity of fluid has long been known [13] to produce oliguria and in some instances complete suppression of urine. Allen [13] has shown that it is only in the severely diabetic organism that dextrose administered in any other way than intravenously produces polyuria rather than an antidiuretic effect. The stimulation of renal activity afforded by the large amounts of urea and water might be expected to overcome this oliguria, but even when the depressed volumes of urine are still reasonably high we have found a marked decrease in the degree of renal activity as measured by the urine-blood urea relationship following the ingestion of 100 Gm. or more of dextrose under these conditions. Since we desired to avoid this and as many of the subjects did not have severe diabetes, dextrose was administered intravenously. The procedure for each experiment was essentially as follows:

The subjects were given no food or fluids for a period of twelve hours preceding the determinations. Each subject was given approximately 0.25 Gm. of urea and 20 cc. of water per kilogram by mouth at 6 a. m. Ten cubic centimeters

11. Addis, T.: The Ratio Between the Urea Content of the Urine and of the Blood After the Administration of Large Quantities of Urea, J. Urol. **1**:263, 1917.

12. Addis, T., and Drury, D. R.: The Effect of Changes in Blood Urea Concentration on the Rate of Urea Excretion, J. Biol. Chem. **55**:105, 1923.

13. Allen, F. M.: Studies Concerning Glycosuria and Diabetes, Cambridge, Mass., Harvard University Press, 1913, chap. 6. Sherrill, J. W., and John, H. J.: The Influence of Glucose Ingestion on Diuresis and Blood Composition in Non-Diabetic or Diabetic Persons, J. Metab. Research **1**:109, 1922.

of water per kilogram of body weight was given each hour thereafter until the observations were ended. By 9 a. m. full renal activity with good diuresis had been established, and from 25 to 50 Gm. of dextrose in 50 per cent solution was given intravenously through one of the superficial veins of the arm. All intervals on the chart were measured from this point. The patient at once emptied his bladder completely, and specimens of urine were saved after this. They were collected at 30, 60, 90, 120, 150, 180, 210 and 240 minutes. Specimens of blood were taken at the middle of each period of urine collection, that is, at 15, 45, 75, 105, 135, 165, 195 and 225 minutes after the ingestion of dextrose. The subject remained in bed throughout the test and received no other fluid, food or medication during this period.

The determinations of the blood sugar were made by the micromodification of the Shaffer-Hartman method suggested by Somogyi.[14] By the use of Somogyi's zinc sulphate reagents[15] for removing the blood proteins, the nonfermentable reducing substances were removed from the filtrate at the same time. Samples of blood of 0.2 cc. each were collected in a long, accurate 15 cm. calibrated capillary pipet and washed out with the diluting fluid. The blood was obtained by a

TABLE 1.—*Results of a Typical Experiment on Determination of the Renal Threshold for Dextrose*

Urine Collected			
Time, Min.	Volume Rate, Cc. per Hr.	Dextrose Excreted, Mg. per Hr.	Blood Dextrose, Mg. per 100 Cc.
30	920	2,520	280
30	330	465	219
30	430	196	184
30	600	18	149
30	490	9	107
30	550	0	68
Dextrose threshold			128 mg.

clean deep prick of the finger with a sharp lancet after the hand had been held for some minutes in hot water.

The fermentable reducing substances of the urine were determined by a modification of the Shaffer-Hartman method,[16] yeast fermentation being used for the removal of nonsugar substances. With our dilute urines the dilution described by the authors was unnecessary.

RESULTS

With the very rigid methods that have been described as ideal for determining the renal threshold for dextrose, observations have been made on ten persons with diabetes and eleven patients without known abnormalities in their carbohydrate metabolism and apparently with normal kidneys. A typical experiment is presented in table 1. The observations from each experiment necessary for determining the threshold form table 2. We have assumed for present purposes that a

14. Shaffer, P. A., and Somogyi, M.: Copper-Iodometric Reagents for Sugar Determination, J. Biol. Chem. **100**:695, 1933.

15. Somogyi, M.: A Method for Preparation of Blood Filtrates for the Determination of Sugar, J. Biol. Chem. **86**:655, 1930.

16. Harding, V. J., and Van Nostrand, F. H.: Variations in Blood and Urinary Sugar After the Ingestion of Galactose, J. Biol. Chem. **85**:765, 1930.

TABLE 2.—*Observations from Each Experiment Necessary to Determine the Renal Threshold for Dextrose*

No.	Period, Min.	Urine Volume, Cc. per Hr.	Urine Dextrose, Mg. per Hr.	Blood Dextrose, Mg. per 100 Cc.
N. D. 1	30	530	495	180
	30	530	0	134
2	30	280	200	190
	30	410	11	152
	30	470	0	140
3	30	750	67	154
	30	500	0	121
4	30	430	196	184
	30	600	18	149
	30	490	9	107
	30	550	0	68
5	30	470	117	171
	30	450	41	162
	30	520	0	94
6	30	480	170	168
	30	520	8	64
	30	660	0	56
7	30	300	378	112
	30	340	7	99
	30	390	0	86
8	30	400	200	196
	30	620	12	104
	30	610	0	98
9	30	520	37	132
	30	450	15	104
	30	710	0	96
10	30	390	776	109
	30	320	12	95
	30	300	0	71

No.	Period, Min.	Urine Volume, Cc. per Hr.	Urine Dextrose, Mg. per Hr.	Blood Dextrose, Mg. per 100 Cc.
D 1	30	140	81	210
	30	160	30	173
	30	70	9	158
2	30	230	510	194
	30	640	4	130
3	30	690	1,692	211
	30	700	300	197
	30	610	12	163
	30	580	0	160
4	60	200	32	179
	30	660	7	158
	30	610	0	149
5a	30	510	41	162
	30	430	0	150
5b	30	280	1,316	193
	30	530	22	157
	30	610	0	152
5c	30	470	301	271
	30	520	62	163
	30	410	0	133
6a	30	110	10	182
	30	420	5	124
6b	30	630	196	178
	30	640	52	150
	30	580	4	134
6c	30	170	46	163
	30	230	11	142
	30	640	4	133
7	45	390	68	157
	30	320	0	135
8	30	230	560	193
	30	160	71	160
	30	240	3	132
9	30	270	18	151
	30	190	0	111
10	30	720	1,210	173
	30	680	68	146
	30	530	0	98

TABLE 3.—*Renal Threshold for Dextrose in a Group of Persons with Diabetes and a Group Without Diabetes*

Case	Sex	Age, Years	Dextrose Threshold	Comment
			Persons Without Diabetes	
1	F	32	157	Bronchiectasis
2	M	50	146	Mild hypertension
3	F	55	138	Normal
4	F	14	128	Mild obesity
5	F	53	128	Thyropituitary obesity
6	F	50	116	Hypertension
7	F	71	106	Hypertension
8	F	43	101	Obesity
9	F	55	100	Past undernutrition
10	F	55	83	Asthma
11	M	61	78	Normal
			Diabetic Patients	
1	F	70	165	Severe diabetes
2	M	67	162	Severe diabetes; 10 years' duration
3	F	59	161	Moderate severity; 2 years' duration
4	M	67	160	Mild diabetes; 2 months' duration
5a	F	51	156	Severe diabetes
5b	F	51	154	
5c	F	51	148	
6a	M	14	153	Mild diabetes
6b	M	16	142	
6c	M	16	138	
7	F	55	146	Mild type
8	F	74	146	Severe diabetes; 8 years' duration
9	F	22	131	Moderate severity; 2 years' duration
10	F	58	122	Trivial diabetes for 1 year

urine containing 10 mg. or less of dextrose per hour is sugar-free. The analytic methods in our hands make the measurement of this amount questionable. We have chosen as the renal threshold for dextrose the average of the midperiod values for blood dextrose for the last period in which sugar was found in the urine and for the first period in which there was no sugar. Certain pertinent data and the renal thresholds for dextrose are presented in table 3.

With the particular groups which were examined the renal threshold for dextrose was on the average definitely higher in persons with diabetes than in those who did not have diabetes. The average for the former group was 149 mg. per hundred cubic centimeters in comparison with 128 mg. for the latter group. There was a large degree of variability in both groups. In the two persons (D5 and D6) for whom repeated determinations were made a rather good degree of constancy was found.

CONCLUSIONS

These experiments and our consideration of the factors involved in the determination of the renal threshold for dextrose lead us to the conclusion that the threshold as a "normal figure" is a misnomer. That a given subject has his own particular level above which sugar appears in the urine is probable, provided the conditions are the same each time. Under ordinary circumstances the figure found simply represents the situation as it exists at that particular moment. A normal average for the renal threshold should never be given, for it may be misleading.

For practical purposes the renal threshold for dextrose is of clinical interest only when dextrose is detected in the urine, for this indicates either hyperglycemia or a so-called "renal diabetes." In the absence of sugar in the urine qualitatively the renal threshold has no place.

EFFECT OF LOW CALORIC DIETS AND RESULTANT LOSS IN WEIGHT ON PLASMA CHOLESTEROL IN THE OBESE

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In a previous communication [1] we showed that in obese subjects in whom evidence of metabolic disorders (diabetes mellitus, including the prediabetic state, essential hypertension and arteriosclerosis) and arthritic disturbances (osteo-arthritis) was lacking the cholesterol content of the plasma was usually at a normal level. The advent of these degenerative diseases in the obese was generally accompanied by a rise in the plasma cholesterol.

The second phase of the problem, namely, a study of the variations in the blood cholesterol in obese subjects undergoing reduction of weight on a low caloric diet, is now reported. We wished to determine whether loss in weight while on a low caloric diet exerted any influence on the normal level of the plasma cholesterol in subjects with uncomplicated obesity and, again, whether the elevated plasma cholesterol in obese persons showing evidence of degenerative disease could be reduced by a similar diet.

MATERIAL AND METHODS

Thirty subjects, chosen at random from our original group of ninety-four, were placed on a low caloric diet, and the body weight and plasma cholesterol were determined at more or less regular intervals for from six to sixty weeks. Table 1 indicates the cases studied (the numbers of the cases conform with those employed in our previous paper [1] and represent the same subjects), the original weight, the percentage overweight, the length of the study, the number of determinations of cholesterol and the loss in weight. The average patient weighed 207 pounds (94.1 Kg.), was 49.6 per cent overweight, and lost 20 pounds (9.1 Kg.) during twenty-two weeks of observation; nine determinations of cholesterol were made serially.

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1. Bruger, M., and Poindexter, C. A.: Relation of the Plasma Cholesterol to Obesity and to Some of the Complicating Degenerative Diseases (Diabetes Mellitus, Essential Hypertension, Osteo-Arthritis and Arteriosclerosis), Arch. Int. Med. **53**:423 (Feb.) 1934.

The subjects were ambulatory and were followed in the clinic for obese patients of the New York Post-Graduate Hospital. Without exception, all venipunctures were carried out in the morning, in most cases after the patient had partaken of the prescribed breakfast.

The cholesterol content of the plasma was determined by Sackett's modification of the Bloor method,[2] with the temperature control procedure employed in this laboratory for colorimetric estimation.[3]

TABLE 1.—*Original Weight, Percentage Overweight, Length of Study, Number of Determinations of Plasma Cholesterol and Loss in Weight on a Low Caloric Diet in Fourteen Cases of Uncomplicated Obesity and in Sixteen Cases of Obesity Complicated by Metabolic, Arthritic or Endocrine Disturbances, Which Form the Basis for the Present Study*

Case	Class	Original Weight, Pounds	Percentage Overweight	Length of Study, Weeks	Number of Cholesterol Determinations	Loss of Weight, Pounds
2	Uncomplicated	164	23.3	10	5	8
10	Uncomplicated	172	27.4	20	16	22
14	Uncomplicated	194	32.9	7	4	9
21	Uncomplicated	211	40.6	6	4	13
22	Uncomplicated	183	43.0	25	4	27
23	Uncomplicated	172	43.3	10	6	16
26	Uncomplicated	265	46.4	23	5	28
27	Uncomplicated	197	48.1	20	11	30
32	Uncomplicated	231	56.0	13	5	10
37	Uncomplicated	216	58.8	41	9	28
38	Uncomplicated	209	59.5	23	6	13
41	Uncomplicated	193	60.8	29	8	35
49	Uncomplicated	224	80.7	12	3	16
53	Uncomplicated	292	107.0	10	7	38
56	Metabolic	192	28.0	60	24	28
59	Metabolic	187	29.9	11	6	12
60	Metabolic	182	30.9	22	16	12
62	Metabolic	194	34.7	13	4	14
64	Metabolic	168	35.5	9	4	5
66	Metabolic	168	37.7	53	39	16
71	Metabolic	188	46.7	16	7	12
73	Metabolic	233	64.1	17	5	12
76	Metabolic	225	70.5	32	4	16
77	Metabolic	298	122.3	33	9	42
80	Arthritis	175	22.4	9	5	10
83	Arthritis	173	31.1	13	6	3
84	Arthritis	197	36.8	50	17	37
85	Arthritis	187	39.6	13	5	22
92	Endocrine	227	65.7	22	10	17
93	Endocrine	280	65.7	27	11	49
	Average	207	49.6	22	9	20

RESULTS

Table 2 indicates the results obtained in fourteen cases of uncomplicated obesity. It is significant from this protocol that reduction in weight is not accompanied by any uniform trend of the plasma cholesterol content; in general, marked loss in weight in the obese is usually associated with no alteration in the cholesterol content of the plasma (cases 23, 26, 27, 37, 41 and 53).

2. Sackett, G. E.: Modification of Bloor's Method for Determination of Cholesterol in Whole Blood or Blood Serum, J. Biol. Chem. **64**:203, 1925.

3. Mirsky, I. A., and Bruger, M.: A Note on the Liebermann-Burchard Color Reaction for Cholesterol, J. Lab. & Clin. Med. **18**:304, 1932.

Two cases were exceptional. In case 10 there was initial hypercholesteremia. With loss in weight on a low caloric diet, there was a suggestive fall in the amount of plasma cholesterol. It is difficult to explain this result unless it is assumed that the patient may have shown

TABLE 2.—*Effect of a Low Caloric Diet and Resultant Loss in Weight on the Plasma Cholesterol in Fourteen Cases of Uncomplicated Obesity* *

Time, Weeks	Cholesterol	Weight	Diet
Case 2			
0	229	164	
3	213	161	1
5	204	157	2
8	248	156	1
10	194	156	2
Case 10			
0	301	174	
1	324	170	1
3	352	170	3
5	347	165	3
7	278	162	3
9	259	159	3
12	263	157	3
14	295	155	3
16	274	151	3
18	295	151	4
20	276	150	4
Case 14			
0	202	194	
3	232	192	5
5	226	189	5
7	192	185	5
Case 21			
0	149	211	
2	143	206	1
4	121	200	1
6	175	198	1
Case 22			
0	216	183	
20	233	158	1
22	245	157	1
25	260	156	1
Case 23			
0	179	172	
2	172	171	None
4	185	165	4
6	174	164	4
8	201	161	4
10	188	156	4
Case 26			
0	147	265	
13	181	243	4
16	199	242	4
19	161	240	4
23	167	237	4
Case 27			
0	192	197	
2	162	193	5
4	175	187	1
6	142	184	1
8	176	180	1
10	149	179	1
12	169	174	1
14	149	170	1
16	221	168	6
19	165	167	6
20	172	167	6
Case 32			
0	216	231	
2	235	231	4
4	180	224	4
8	223	222	1
13	206	221	1†
Case 37			
0	183	216	
2	186	208	5
4	175	199	1
6	155	195	1
7	167	193	1
20	172	187	1
22	156	183	1
24	170	180	1
41	176	188	1†
Case 38			
0	206	209	
1	214	207	5†
8	216	203	5†
10	190	200	5†
13	183	198	5†
23	152	196	5†
Case 41			
0	194	193	
4	204	179	5
6	184	177	5
8	192	173	5
14	230	163	5
17	195	160	1
21	227	159	1
29	226	158	1
Case 49			
0	214	224	
3	179	220	1X
12	248	208	1Y
Case 53			
0	168	294	
1	192	284	None
3	206	278	5
5	173	270	5
7	173	265	5
10	175	254	5

* In tables 2 and 3 the cholesterol is expressed in milligrams per hundred cubic centimeters of plasma and the weight in pounds. The diets employed were as follows:

Diet	Carbohydrate	Protein	Fat	Calories	Diet	Carbohydrate	Protein	Fat	Calories
1	35	70	20	600	5	65	80	40	940
2	45	75	30	750	6	80	80	40	1,000
3	65	79	20	756	7	100	96	56	1,298
4	85	80	25	885					

† This patient was taking food in excess of the prescribed diet.
X indicates 1 grain of thyroid daily; Y, erysipelas; Z, cerebral thrombosis.

impairment of sugar tolerance (so-called prediabetic state), which would account for the initial elevated value for plasma cholesterol, and that the decrease in the cholesterol content was associated with an improvement in carbohydrate tolerance consequent to the ingestion of a low caloric diet and reduction in weight. In case 38 also there was a signifi-

cant fall in the plasma cholesterol content following loss in weight. The subject, however, had rheumatic cardiac disease with mitral stenosis and showed signs of increasing decompensation, which probably accounts for the gradual diminution of the amount of blood cholesterol (a low blood cholesterol content in association with cardiac decompensation is not an uncommon finding).

Table 3 indicates the results obtained in sixteen cases of obesity complicated by metabolic, arthritic and endocrine disturbances. In general, the findings are similar to those just discussed for the uncomplicated group; namely, moderate to marked loss in weight, provided no obvious change has taken place in the complicating disease, is usually associated with no alteration in the cholesterol content of the plasma (cases 59, 60, 62, 71, 76, 77, 84, 92 and 93).

The diminishing blood cholesterol content in cases 56 and 66 accompanying loss in weight can probably be accounted for by change in the clinical status of the patients. In case 56 the patient showed increasing cardiac embarrassment as result of long-standing hypertension; definite signs of cerebral thrombosis became evident forty-six weeks after the study was begun. In case 66 the patient had diabetes and required 8 units of insulin a day on the diet prescribed to keep the urine sugar-free. With loss in weight, the blood sugar content after fasting showed a consistent decrease, the carbohydrate tolerance gradually improved and finally the administration of insulin could be discontinued.

In cases 60, 66 and 83 there was a definite increase in the plasma cholesterol for two or three weeks after the institution of a low caloric diet. The possibility that this finding represents the so-called "starvation effect" will be discussed later.

COMMENT

The results reported in this paper do not lend themselves easily to statistical analysis for the following reasons: In a protracted study of this type in which a single constituent of the blood is investigated at more or less regular intervals for as long as sixty weeks, the existence of variables must be considered. The extent of weekly variations in the amount of blood cholesterol and the existence of seasonal variations, if any, and of premenstrual and menstrual changes are factors which cannot be ignored. The degree of diurnal variations of the blood cholesterol content found by Bruger and Somach [4] indicates that daily and weekly changes are probably marked. In 1924 Currie [5] maintained that marked seasonal variations exist; the presence of such variations, how-

4. Bruger, M., and Somach, I.: The Diurnal Variations of the Cholesterol Content of the Blood, J. Biol. Chem. **97**:23, 1932.

5. Currie, A. N.: The Cholesterol of Blood in Malignant Disease, Brit. J. Exper. Path. **5**:293, 1924.

TABLE 3.—*Effect of a Low Caloric Diet and Resultant Loss in Weight on the Plasma Cholesterol in Sixteen Cases of Obesity Complicated by Metabolic, Arthritic and Endocrine Disturbances* *

Time, Weeks	Cholesterol	Weight	Diet
Case 56 (A)†			
0	326	192	
2	211	189	4
4	215	185	1
7	229	186	1
9	229	184	1
11	286	182	1
13	190	179	1
15	295	176	1
17	204	176	1
23	253	176	1
26	275	174	1
29	257	174	1
32	282	171	1
35	235	174	1
38	240	172	1
43	217	175	1
46	308	170	1Z
48	253	169	1
50	295	172	1
52	232	168	1
54	282	168	1
56	250	168	1
58	229	167	1
60	191	164	1
Case 59 (A, B)			
0	229	187	
3	242	180	5
4	216	182	5†
6	282	178	5
8	214	175	5
11	218	175	5
Case 60 (A, B)			
0	247	182	
1	285	175	Restricted
2	262	174	2
3	332	174	2
4	244	178	2†
5	391	175	2
6	377	174	2
7	364	176	2†
8	344	171	1
9	379	173	3
11	253	170	1
13	244	170	1†
15	244	170	1†
18	259	170	1†
20	276	169	1†
22	272	170	1†
Case 62 (A)			
0	217	194	
2	217	190	None
4	262	186	5
13	242	180	5†
Case 64 (B)			
0	260	168	
1	248	168	5
4	216	164	5
9	255	164	5†
Case 66 (C)			
0	348	168	
1	346	166	3
2	487	166	3
3	444	166	1
4	421	164	1
5	395	162	1
6	399	164	1
7	354	160	1
9	303	157	1
12	286	158	1
14	284	156	1
16	329	155	1
18	226	155	1
20	323	154	1
22	245	153	1
24	295	150	1
26	264	151	1†
28	315	148	1
30	185	145	1
32	201	144	1
35	242	140	1
38	266	144	1†
40	278	145	1†
44	282	145	1†
53	233	152	1†
Case 71 (A)			
0	278	188	
1	259	185	1
3	235	187	1
7	245	184	1
9	308	180	1
14	298	177	1
16	280	176	1
Case 73 (B)			
0	270	233	
2	239	232	1
4	262	228	1
8	262	223	1
17	282	221	1
Case 76 (A)			
0	178	225	
6	250	...	5
10	260	...	5
32	204	209	5†
Case 77 (A)			
0	181	298	
11	166	268	1
17	161	260	1
20	213	260	1
24	195	255	1
26	225	253	1
28	232	257	1†
30	218	252	1
33	232	256	1†
Case 80 (D)			
0	274	175	
2	289	173	5
4	242	169	5
6	223	167	5
9	286	165	5
Case 84 (E)			
0	168	197	
2	187	191	5
4	193	187	5
6	198	183	5
8	169	178	2
10	168	175	2
12	153	173	2
14	207	170	2
18	210	167	2
20	190	166	2
22	187	166	2
27	205	162	2
40	203	159	2
42	192	159	5†
46	175	160	6†
48	194	159	6†
50	193	160	6†
Case 83 (D)			
0	274	173	
2	369	171	1
4	354	169	1
6	252	168	1
8	227	171	7
13	227	170	5†
Case 85 (E)			
0	279	187	
3	230	179	5
6	225	173	5
8	235	170	5
13	178	165	5
Case 92 (F)			
0	161	227	
2	200	229	6
4	180	224	6
6	230	222	1
8	255	218	1
10	173	218	1†
12	175	215	1
19	202	210	1
21	213	210	1†
22	212	210	1†
Case 93 (G)			
0	289	280	
2	198	271	6
4	174	265	7
6	214	264	7
9	216	256	7
11	175	250	7
13	183	246	7
16	233	238	7
20	259	234	7
23	255	231	7
27	200	231	7

* The associated clinical conditions are: (A) essential hypertension; (B) diminished dextrose tolerance curve; (C) diabetes mellitus; (D) osteo-arthritis; (E) rheumatoid arthritis; (F) hypo-ovarian dysfunction; (G) acromegaly.

† This patient was taking food in excess of the prescribed diet.

ever, has been refuted by McEachern and Gilmour.[6] Gonalons,[7] Moynihan,[8] quoting the work of Shiskin, and Okey and Boyden[9] found definite changes immediately preceding and during menstruation. In view of these reports, it seemed futile to attempt a mathematical correlation between body weight and the blood cholesterol content; a study of the trend of the blood cholesterol content with diminishing body weight indicated that no such correlation existed.

Mention has been made that some subjects showed a distinct rise in the plasma cholesterol content for two or three weeks after the institution of a low caloric diet. The assumption was made that this increase may represent the so-called starvation effect. Starvation was found to increase the blood cholesterol in animals by Ellis and Gardner[10] (rabbits), Rothschild[11] (rabbits), Morizawa[12] (rabbits), Mouriquand and Leulier[13] (guinea-pigs), Shope[14] (swine, cats, guinea-pigs and rabbits) and Wendt[15] (dogs) and in human beings by Lennox, O'Connor and Bellinger[16] (in one of three cases) and Shope[14] (one case reported). The variable results reported by Lennox and his collaborators resemble closely our own findings, provided, of course, it

6. McEachern, J. M., and Gilmour, C. R.: Studies in Cholesterol Metabolism: II. Blood Cholesterol in Various Conditions, Canad. M. A. J. **26**:158, 1932.

7. Gonalons, G. P.: Variaciones de la colesterinemia durante el ciclo menstrual, Semana méd. **23**:639, 1916; Variations de la cholestérinémie pendant le cycle menstruel et la lithiase biliaire, Bull. et mém. Soc. méd. d. hôp. de Paris **41**:749, 1917; Litiasis biliar e hipercolesterinemia menstrual, Rev. Asoc. méd. argent. **26**: 1091, 1917.

8. Moynihan, B.: Some Aspects of Cholelithiasis, Brit. M. J. **1**:393, 1925.

9. Okey, R., and Boyden, R. E.: Studies of the Metabolism of Women: III. Variations in the Lipid Content of Blood in Relation to the Menstrual Cycle, J. Biol. Chem. **72**:261, 1927.

10. Ellis, G. W., and Gardner, J. A.: The Origin and Destiny of Cholesterol in the Animal Organism: IX. The Cholesterol Content of the Tissues, Other Than Liver, of Rabbits Under Various Diets and During Inanition, Proc. Roy. Soc. London, s.B **85**:385, 1912.

11. Rothschild, M. A.: Zur Physiologie des Cholesterinstoffwechsels: V. Der Cholesteringehalt des Blutes und einiger Organe im Hungerzustand, Beitr. z. path. Anat. u. z. allg. Path. **60**:227, 1914-1915.

12. Morizawa, K.: Cholesteringehalt des Blutes von Hungerkaninchen, Acta scholae med. Univ. imp. in Kioto **7**:349, 1924-1925.

13. Mouriquand, G., and Leulier, A.: Inanition et cholestérine du sang et de quelques organes chez le cobaye, Compt. rend. Soc. de biol. **94**:533, 1926.

14. Shope, R. E.: Sugar and Cholesterol in the Blood Serum as Related to Fasting, J. Biol. Chem. **75**:101, 1927.

15. Wendt, H.: Lipoidstoffwechselstudien am Hungertier, Klin. Wchnschr. **7**:2183, 1928.

16. Lennox, W. G.; O'Connor, M., and Bellinger, M.: Chemical Changes in the Blood During Fasting in the Human Subject, Arch. Int. Med. **38**:553 (Nov.) 1926.

is safe to assume that the ingestion of a low caloric diet (about 600 calories) by persons accustomed to a high caloric intake represents starvation in a relative sense.

CONCLUSIONS

The cholesterol content of the plasma in uncomplicated obesity and in obesity complicated by metabolic, arthritic or endocrine disease is not altered primarily by reduction in weight with a low caloric diet.

At times, the initial high plasma cholesterol content of the obese patient with complicating degenerative disease may show a significant decrease following reduction of weight on a low caloric diet. This fall in the blood cholesterol content is due not to a diminution in body weight but secondarily to changes in the clinical condition of the patient (improvement in carbohydrate tolerance in the obese patient with diabetes mellitus, onset of cardiac decompensation in the obese patient with hypertension, etc.).

In some obese subjects, the institution of low caloric diets is accompanied by a definite increase in the amount of plasma cholesterol for two or three weeks. The assumption is made that this elevation of the blood cholesterol content represents the so-called starvation effect, an observation that has been recorded previously in man and in animals.

EFFECT OF CERTAIN THERAPEUTIC MEASURES ON THE CARDIAC OUTPUT OF PATIENTS WITH CONGESTIVE HEART FAILURE

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An investigation of the change in the amount of blood pumped by the failing heart following the institution of a therapeutic procedure may be of interest from two points of view: (*a*) from the standpoint of the pathogenesis of congestive heart failure and (*b*) from the standpoint of the mechanism whereby a given procedure produces improvement. The present study was undertaken with the idea of elucidating the first of these problems, but certain information concerning the second question has also been obtained.

METHOD

The subject—in the basal state—was brought to the laboratory in a wheelchair. The consumption of oxygen was determined in duplicate by analyses of samples of the expired air which was collected in a Tissot spirometer. The arteriovenous oxygen difference was measured by the three sample acetylene technic. Two rebreathings were usually done, the samples being procured at approximately twenty, twenty-four and twenty-eight seconds in the first, and two seconds later in the second. When the two successive values for the arteriovenous difference obtained during a single rebreathing failed to agree within 10 per cent, the determination was discarded. Further details of the technic employed are given in previous studies.[1]

Following one or more measurements of the cardiac output the desired therapeutic procedure was instituted. In those cases in which the effect of rest was studied the subject was kept in bed, fluids were restricted and no medication was administered other than sedatives when necessary and maintenance doses of digitalis when the subject had already been receiving this drug. After several days of this regimen the measurements were repeated. A similar plan was fol-

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1. Grollman, A.; Friedman, B.; Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure: XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, J. Clin. Investigation, **7**:751, 1933. Harrison, T. R.; Friedman, B.; Clark, G., and Resnik, H., Jr.: Cardiac Output in Relation to Cardiac Failure, Arch. Int. Med. **54**:238 (Aug.) 1934.

lowed in the case of the other therapeutic procedures. In the observations on the effect of venesection, several measurements of the cardiac output were made in one day, and some of the determinations were made several hours after the ingestion of a glass of milk. With these exceptions all observations were made on the subject in a strictly basal state.

RESULTS

Rest.—In table 1 are shown the data on four patients. Following two or more days of rest the vital capacity rose in three subjects, and diuresis occurred in two. Subjective improvement occurred in three of the four patients. A significant decline in oxygen consumption occurred in one instance. The cardiac output decreased in two of the subjects. In proportion to the metabolism the cardiac output decreased in two persons and was unchanged in the others. (Alterations in the cardiac output and in the arteriovenous oxygen difference of less than 10 per cent are not considered significant, for the error of the method may be this great.) No correlation existed between clinical improvement and the changes in cardiac output.

The changes in cardiac output and in oxygen consumption which occurred following rest are not to be ascribed to the patients' becoming accustomed to the procedures involved, for the subjects had been trained to the methods prior to the beginning of our observations.

Venesection.—Four observations were made on three patients (table 2). Each subject claimed that dyspnea was benefited by the procedure. The vital capacity tended to be greater and the ventilation to be less following bleeding. The cardiac output per minute was decreased in three of the four observations. A temporary decrease in this function in proportion to the metabolism was observed in three instances and the reverse effect in one.

Two striking effects of venesection were noted. The subjects were bled while sitting in a wheelchair. Two of them fainted. As circulatory collapse came on, each subject mentioned that he felt less dyspneic. It was interesting to note that the congestive manifestations—venous distention and dyspnea—became less marked as the phenomena of peripheral circulatory failure—weakness, pallor and fainting—became more marked. In the subjects who fainted, a striking decline in the cardiac output occurred.

Another surprising effect of venesection, which occurred in three of the four observations, was a sharp decrease in the oxygen consumption. This was most striking in the two subjects who prior to bleeding had a marked elevation in the metabolic rate. In order to study this phenomenon more closely, observations were made of the effect on the oxygen consumption of reinfusion of the previously removed blood

TABLE 1.—*Effect of Rest on the Cardiac Output and on the Other Functions of Patients with Congestive Heart Failure*

									Oxygen	Arterio-venous	Cardiac

TABLE 1.—*Effect of Rest on the Cardiac Output and on the Other Functions of Patients with Congestive Heart Failure*

Subject	Diagnosis	Date	Dyspnea*	Edema	Body Weight, Pounds	Vital Capacity, Liters	Cardiac Rate	Oxygen Consumption per Minute, Cc.	Arteriovenous Oxygen Difference per Liter, Cc.	Cardiac Output per Minute, Liters	Clinical Improvement
A. M.	Syphilitic aortic insufficiency	10/14/33	+++	+++	179	2.35	92	271	128	2.11	Definite
		10/16/33	++	++	173	2.60	84	245	120	2.04	
G. M.	Syphilitic myocarditis	9/ 7/33	++	++	150	1.75	75	232	66	3.49	Definite
		9/13/33	+	+	137	2.10	78	241	75	3.19	
A. T.	Mitral stenosis	7/22/33	++	++	96	1.70	82	186	87	2.13	Questionable
		7/25/33	+	++	96	1.80	100	200	107	1.88	
R. O.	Hypertension	2/18/33	+	0	136	2.75	82	187	68	2.74	None
		2/22/33	+	0	135	2.70	88	178	74	2.41	

* In this and the following tables the symbols +, ++ and +++ refer respectively to dyspnea on exertion only, mild dyspnea at rest, and moderate dyspnea at rest.

TABLE 2.—*Effect of Venesection on the Cardiac Output and Other Functions of Patients with Congestive Heart Failure*

Subject	Diagnosis	Date	Dyspnea	Edema	Time in Relation to Venesection	Vital Capacity, Liters	Ventilation per Minute, Liters	Oxygen Consumption per Minute, Cc.	Arteriovenous Oxygen Difference per Liter, Cc.	Cardiac Output per Minute, Liters	Clinical Improvement	Comment
F. B.	Syphilitic aortic insufficiency	6/27/33	+++	++	Before	1.85	15.2	403	110	3.66		
			++	++	30 min. after	....	12.6	374	109	3.41	Slight	500 cc. blood removed
			+	++	2 hr. after	1.90	12.5	324	95	3.42	Slight	
			+	++	6 hr. after	1.99	14.8	351	112	3.14	Slight	
		6/28/33	+	++	1 day after	1.90	13.5	362	120	3.01	Slight	
L. W.	Mitral stenosis	6/21/33	+++	+	Before	2.85	8.3	235	72	3.29	.....	500 cc. blood removed; patient fainted immediately after
		6/22/33	+++	+	Before	2.90	9.5	240	75	3.21		
			+	+	40 min. after	3.10	10.7	222	86	2.58	Marked	
			+	+	2 hr. after	3.25	9.8	194	72	2.69	Marked	
			+	+	8 hr. after	3.30	8.7	233	73	3.19	Marked	
		8/ 1/33	+++	+	Before	2.95	6.8	197	74	2.69		
			+	+	30 min. after	3.15	7.3	202	82	2.45	Moderate	565 cc. blood removed
			+	+	1 hr. after	3.10	6.9	209	82	2.52	Moderate	
		8/ 2/33	++	+	1 day after	3.00	8.7	239	71	3.38	Slight	
M. O.	Hypertension	8/14/33	++	+	Before	3.70	10.8	331	96	3.43		
			+	+	90 min. after	3.70	8.9	327	112	2.77	Slight	350 cc. blood removed; patient fainted
			+	+	3 hr. after	3.70	8.7	227	105	2.15	Moderate	
		8/15/33	+	+	1 day after	3.90	12.6	353	99	3.57	Moderate	

(fig. 1). In the one patient so studied venesection caused a sharp diminution in the oxygen consumption, which returned to the previous level following the administration of the blood. (Further discussion of the mechanism of the changes in metabolic rate in relation to venesection is beyond the scope of this paper. The problem is dealt with in more detail in a publication by Resnik and Friedman.[2])

Morphine.—Two subjects were studied. In each instance the dyspnea, moderately severe before treatment, was relieved. The pulse rate diminished somewhat, the ventilation declined sharply. Parallel diminution of oxygen consumption and cardiac output occurred, the arteriovenous oxygen difference being unaffected (table 3).

Quinidine.—Three sets of observations were made on two patients who had auricular fibrillation and minimal congestive failure (table 4).

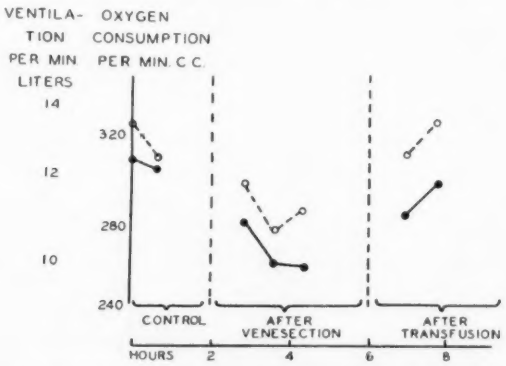

Fig. 1 (F. B.).—Venesection produced a marked decrease in the ventilation and in the oxygen consumption of the patient with syphilitic aortic insufficiency. When the blood which had been removed was reinfused, these effects were reversed. The white circles joined by lines indicate the ventilation per minute; the black circles, the oxygen consumption per minute.

In each instance the administration of quinidine was followed by restoration of the normal mechanism and an increase in the cardiac output. These results are similar to those reported by Smith, Walker and Alt,[3]

2. Resnik, H., Jr., and Friedman, B.: Studies on the Mechanism of the Increased Oxygen Consumption in Persons with Cardiac Disease, J. Clin. Investigation **14**:551, (Sept.) 1935.

3. Smith, W. C.; Walker, G. L., and Alt, H. L.: The Cardiac Output in Heart Disease: I. Complete Heart Block, Auricular Fibrillation Before and After Restoration to Normal Rhythm, Subacute Rheumatic Fever, and Chronic Valvular Disease, Arch. Int. Med. **45**:706 (May) 1930.

TABLE 3.—*Effect of Morphine on the Cardiac Output and on the Other Functions of Patients with Congestive Heart Failure*

Subject	Diagnosis	Date	Dyspnea	Edema	Vital Capacity, Liters	Ventilation per Minute, Liters	Heart Rate	Oxygen Consumption per Minute, Cc.	Arteriovenous Oxygen Difference per Liter, Cc.	Cardiac Output per Minute, Liters	Comment
A. M.	Syphilitic aortic insufficiency	1/ 9/34	++	++	2.60	....	74	235	93	2.53	Before morphine
			+	++	2.70	....	70	208	96	2.17	Two hours after 0.02 Gm. morphine
F. B.	Syphilitic aortic insufficiency	2/28/34	+++	+++	1.50	11.3	108	320	122	2.62	Before morphine
			+	+++	1.50	8.6	96	278	116	2.41	One hour after 0.015 Gm. morphine

TABLE 4.—*Effect of Quinidine on the Cardiac Output and Other Functions*

Subject	Date	Dyspnea	Edema	Vital Capacity, Liters	Heart Rate	Pulse Rate	Oxygen Consumption per Minute, Cc.	Arteriovenous Oxygen Difference per Liter, Cc.	Cardiac Output per Minute, Liters	Comment	
R. R.	9/12/33	+	0	3.30	76	76	311	89	3.50	Fibrillating	Digitalized throughout
	9/13/33	+	0	3.30	80	80	283	90	3.14	Before administration of quinidine	
	9/14/33	+	0	3.50	76	76	282	87	3.26		
	9/18/33	+	0	3.50	66	66	267	60	4.41	Regular	
	9/19/33	+	0	3.10	79	79	255	65	3.95	Premature beats — Receiving quinidine	
	9/20/33	+	0	3.45	66	66	260	67	3.85	Regular	
	2/ 2/34	++	0	3.00	124	102	306	99	3.10	Fibrillating; before digitalis	Before quinidine
	2/ 5/34	+	0	3.45	88	88	285	100	2.85	Fibrillating; digitalized	
	2/ 8/34	+	0	3.45	80	80	2.1	89	3.05	Fibrillating; digitalized	Receiving quinidine
	2/12/34	+	0	3.50	56	56	251	77	3.24	Regular; digitalized	
	2/15/34	+	0	3.50	64	64	283	80	3.53	Premature beats; digitalized	
	2/20/34	+	0	3.20	64	64	265	69	3.83	Regular; digitalized	
L. L.	5/ 4/33	++	0	2.10	72	72	179	89	2.00	Fibrillating; before quinidine	Digitalized throughout
	5/ 6/33	+	0	2.20	72	72	180	82	2.18	Regular; receiving quinidine	
	5/ 8/33	+	0	2.35	76	76	196	84	2.33	Regular; receiving quinidine	

using the carbon dioxide method, and by Kerkhof and Bauman,[4] with the two sample acetylene technic. In proportion to the metabolism the change in cardiac output was slight in subject L. L. but was striking at the time of each observation in subject R. R. In the second group of observations on the latter subject it is interesting to note that clinical improvement, as shown by rise in vital capacity and decrease in dyspnea, occurred following the administration of digitalis without a significant change in the cardiac output. (This is in accord with our previous findings with digitalis.[5]) The increase in cardiac output which followed the administration of quinidine was not accompanied by any striking clinical effect other than the change in rhythm.

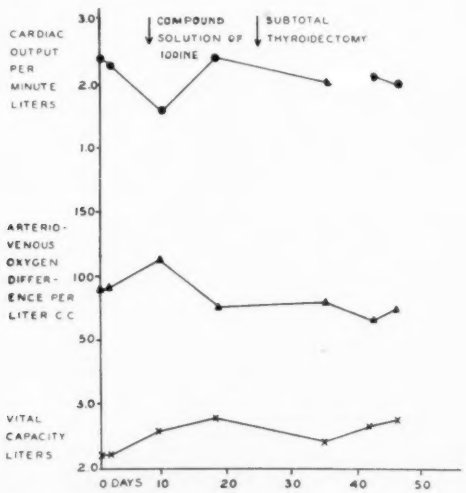

Fig. 2 (A. C.).—The administration of compound solution of iodine was followed by a temporary decline in the cardiac output of the patient with thyrotoxicosis. Following partial thyroidectomy the output again declined and remained below the preoperative level. In proportion to the metabolism the cardiac output increased after the operation. The rise in vital capacity paralleled the clinical improvement.

Subtotal Thyroidectomy.—One patient who had cardiac failure secondary to thyrotoxicosis was studied (fig. 2). After the administration

4. Kerkhof, A. C., and Bauman, H.: Minute Volume Determinations in Mitral Stenosis During Auricular Fibrillation when Restored to Regular Rhythm, Proc. Soc. Exper. Biol. & Med. **31**:168, 1933.

5. Friedman, B.; Clark, G.; Resnik, H., Jr., and Harrison, T. R.: Effect of Digitalis on the Cardiac Output of Persons with Congestive Heart Failure, Arch. Int. Med., to be published.

of compound solution of iodine, U. S. P., there was a marked temporary decline followed by a rise in the cardiac output. After subtotal thyroidectomy the cardiac output was slightly less, but considerably greater in proportion to the metabolism, than before the operation. Clinical improvement, as shown by decrease in dyspnea and rise in vital capacity, was striking after the administration of compound solution of iodine and persisted after the operation.

Total Thyroidectomy.—Levine,[6] Blumgart [7] and their co-workers recommended total ablation of the thyroid gland in persons with irreducible congestive heart failure. In this clinic only one patient has been so treated.

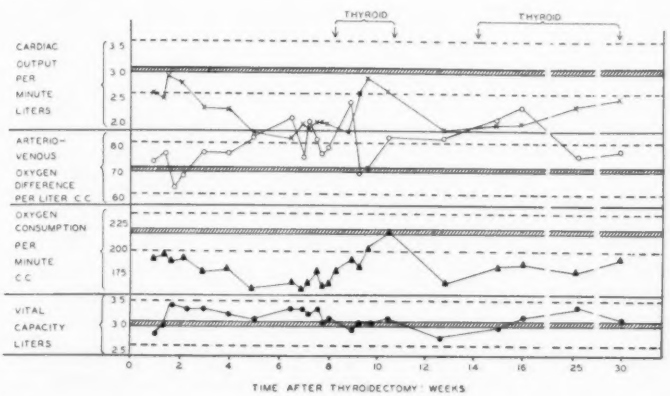

Fig. 3.—The shaded areas represent the averages and the dotted lines indicate the ranges of the various functions in the fifteen observations made before operation. All the points charted designate postoperative measurements. Following total thyroidectomy the vital capacity tended to be somewhat greater. The oxygen consumption and the cardiac output were considerably diminished. The changes in the arteriovenous oxygen difference were inconstant, but this function tended to be somewhat increased, indicating a diminution in the cardiac output in proportion to the metabolism.

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6. Levine, S. A.; Cutler, E. C., and Eppinger, E. C.: Thyroidectomy in Treatment of Advanced Congestive Heart Failure and Angina Pectoris, New England J. Med. **209**:667, 1933.

7. Blumgart, H. L.; Levine, S. A., and Berlin, D. D.: Congestive Heart Failure and Angina Pectoris: The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity, Arch. Int. Med. **51**:866 (June) 1933; Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris: III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity, ibid. **52**: 165 (Aug.) 1933.

L. W., a 52 year old mechanic, was first admitted to the Vanderbilt University Hospital in March 1931, complaining of orthopnea, paroxysmal dyspnea and slight edema of the legs of one month's duration. The patient had rheumatic fever at the age of 20 at which time he was told that his heart had been affected. He was free from symptoms until June 1930, when he began to have dyspnea on exertion, gradually becoming more severe. At the time of entry there was evidence of rheumatic heart disease with mitral stenosis, auricular fibrillation and cardiac enlargement.

With digitalization he had temporary improvement, but the symptoms returned with such severity as to require hospitalization in October 1931. In July 1932 he reentered the hospital, because of orthopnea, paroxysmal dyspnea, cough and expectoration, and in addition to cardiac decompensation his condition was diagnosed as bronchopneumonia, which resulted in a rather extensive bronchiectasis.

In June 1933 he was admitted again, because of congestive heart failure, but three weeks after discharge further hospitalization was found necessary. Again relief was very temporary, and in August 1933 he was readmitted for the fifth time, because of cardiac decompensation.

Despite restriction of activity, limitation of fluids and the use of digitalis and diuretics, it was apparent that the patient's cardiac reserve had diminished to such an extent that he was unable to remain at home in comfort, although in the hospital it was possible to keep him comparatively free from symptoms. As another therapeutic measure total ablation of the thyroid was proposed, the risk of which the patient readily consented to undertake. On Sept. 12, 1933, this operation was performed by Dr. Alfred Blalock.

After one week the patient felt so much improved that he was able to sleep almost flat in bed after being up and about for most of the day. This improvement persisted until the end of October 1933, when he began to have paroxysms of dyspnea, slight edema, drowsiness and abdominal distention. With hospitalization and the temporary administration of small doses of thyroid extract, he showed considerable improvement. Three weeks after discharge, on Dec. 14, 1933, readmission was considered advisable because of a recurrence of severe dyspnea, and again in January 1934 it was necessary to hospitalize the patient for treatment of cardiac decompensation as well as profound hypothyroidism. He then entered on a period of five months during which time his distressing symptoms disappeared, except for slight dyspnea and edema that did not prevent him from being up and about all day at home or from taking brief walks outdoors. During this interval he received small doses of thyroid extract, and although he had evidence of cardiac failure he was much more comfortable than he had been during the four months prior to operation, at which time his condition was becoming progressively worse. In May 1934 the dyspnea again became severe enough to require hospitalization.

The patient appeared to be improved following the operative procedure. The beneficial effects were not remarkable but were definite. His vital capacity was slightly greater, and his ventilation was definitely less than before the procedure. The quotient $\frac{\text{ventilation}}{\text{vital capacity}}$, which has been shown[8] to run parallel to the degree of cardiac dyspnea, was diminished by the procedure, and he complained less of dyspnea.

8. Harrison, T. R.; Turley, F. C.; Jones, E., and Calhoun, J. A.: Congestive Heart Failure: X. The Measurement of Ventilation as a Test of Cardiac Function, Arch. Int. Med. **48**:377 (Sept.) 1931.

Of especial interest are the changes in oxygen consumption and in cardiac output. The former declined from the average preoperative value of 220 to 160 cc. per minute. During this period an even greater decrease in cardiac output occurred, the arteriovenous oxygen difference being somewhat greater than the average value before operation. Thyroid was then given, and the oxygen consumption and the cardiac output increased to their preoperative levels. When replacement therapy was discontinued, the values again declined. Readministration of thyroid, in smaller doses, was followed by a slight increase in the oxygen consumption and in the cardiac output. The optimum level for these functions appeared to be about 20 per cent below the preoperative values.

Abdominal Paracentesis.—One patient was studied (table 5). After the withdrawal of fluid from the abdomen the patient experienced marked relief from dyspnea. The associated decline in oxygen consumption was probably due to the diminution in respiratory effort. A parallel decrease in cardiac output occurred. In this connection, it is interesting to note that Brams and Golden [9] demonstrated a decline in venous pressure following abdominal paracentesis in patients with cirrhosis of the liver.

Resection of the Pericardium.—A subject with obliterative pericarditis, which led to an increase in venous pressure and congestive phenomena, was studied before and after partial resection of the pericardium. The history of this patient is being reported in detail by Burwell and Flickinger.[10] Before operation he was bedridden because of anasarca. Following the removal of a portion of the pericardium by Dr. Alfred Blalock marked improvement occurred, and he is now able to lead a relatively normal life. His improvement has been attended by a decline in the arteriovenous oxygen difference and a marked increase in the cardiac output (table 5).

COMMENT

The observations which have been cited show clearly that the fundamental physiologic alteration responsible for the clinical manifestations of congestive heart failure is not a decrease in the cardiac output, either actually or in proportion to the metabolic needs. When improvement is due to certain therapeutic measures, it may be associated with an increase in this function, but when it is brought about by other procedures, it is associated with the reverse effect. At first sight it may seem surprising that two different measures may each produce benefit and yet apparently exert opposite physiologic effects. There are, however, certain considerations which tend to resolve this apparent paradox.

9. Brams, W. A., and Golden, J. S.: Observations on the Vascular Response to Drainage of Ascites, J. Lab. & Clin. Med. **19**:948, 1934.

10. Burwell, C. S., and Flickinger, Don: Obstructing Pericarditis: Effect of Resection of the Pericardium on the Circulation of a Patient with Concretio Cordis, Arch. Int. Med. **56**:250 (Aug.) 1935.

TABLE 5.—*Effect of Abdominal Paracentesis and of Cardiac Decortication on the Cardiac Output and Other Functions*

Subject	Diagnosis	Therapeutic Procedure Studied	Date	Dyspnea	Anasarca	Vital Capacity, Liters	Heart Rate	Oxygen Consumption per Minute, Cc.	Arteriovenous Oxygen Difference per Liter, Cc.	Cardiac Output per Minute, Liters	Comment
A. T.	Rheumatic mitral disease	Abdominal paracentesis, 3,600 cc.	8/ 4/33	+++	+++	1.85	64	195	98	2.10	Before paracentesis
			8/ 4/33	+	+	*	69	161	101	1.59	6 hours after paracentesis } Distinct
			8/ 5/33	+	+	*	64	169	91	1.82	1 day after paracentesis } improvement
H. C.	Concretio cordis (obliterative internal pericarditis)	Cardiac decortication (Partial resection of the thickened pericardium)	11/24/33	++	+++	2.00	—	207	96	2.16	Before operation
			11/27/33	++	+++	2.00	116	217	104	2.09	
			1/27/34	+	+	*	118	235	92	2.54	After operation, gradual improvement
			2/ 3/34	+	+	*	118	233	74	3.16	
			2/ 6/34	+	+	*	114	228	80	2.86	
			2/21/34	0	±	2.10	108	271	72	3.79	

* The vital capacity could not be measured accurately because of the pain produced in the wound by breathing.

Aside from pericardial resection, which is employed for a condition which differs both anatomically and functionally from the usual type of congestive heart failure, the therapeutic measures which have been studied appear to fall into three groups:

1. After certain procedures improvement is accompanied by a decrease in the work [11] of the heart. Examples of such procedures are rest, venesection, sedatives, as exemplified by morphine, and abdominal paracentesis. These measures tend to decrease the respiratory effort by diminishing the ventilation directly (morphine), by lowering the metabolism (rest) or by decreasing the reflex stimulation of breathing (venesection or abdominal paracentesis). The lessened respiratory effort tends in itself to decrease the oxygen consumption, as has been shown by Resnik and Friedman.[2] In severely dyspneic patients the decline in metabolism so produced may be of considerable magnitude. Aside from the decline in metabolism, these various therapeutic measures may lessen the work of the heart by causing a decrease in the venous return and in the cardiac output in proportion to the metabolism.

2. After certain other procedures improvement is accompanied by what appears to be an increase in the mechanical efficiency of the heart. Thus, the reversion to the normal mechanism following the administration of quinidine tends to make the heart more efficient because pulse deficit is eliminated and the rate is slowed, and possibly also because auricular contraction is reestablished.[12] Similarly, the most important effect of digitalis appears to be, as has been pointed out elsewhere,[5] its action in increasing cardiac efficiency.

3. It is probable that after some therapeutic measures benefit is accompanied both by decrease in the work of the heart and by increase in its efficiency. Thyroidectomy diminishes the work performed by the

11. The work of the heart is not dependent on the output alone. The blood pressure and the velocity imparted to the blood are also factors. However, the velocity is, under conditions of low output, of minor import. Since our patients have not shown an increase in blood pressure as improvement occurred—the reverse effect has sometimes been observed—it is justifiable to speak of a decrease in work when the output has declined.

12. The effect of a pulse deficit in making the heart inefficient is obvious, for each beat which does not reach the periphery is wasted. For a given amount of work per minute the heart is more efficient at slow than at rapid rates, because during tachycardia the semilunar valves have to be opened more frequently and the energy so expended is not used in expelling blood. It has been demonstrated by Evans and Matsuoka that the oxygen consumed by the heart is greater at rapid than at slow rates, the amount of work being kept constant (Evans, C. L., and Matsuoka, Y.: The Effect of Various Mechanical Conditions on the Gaseous Metabolism and Efficiency of the Mammalian Heart, J. Physiol. **49**:378, 1915).

heart, and the slower cardiac rate after the operation would be expected to produce an increase in mechanical efficiency.

The energy expended by the heart is related to two factors: the work accomplished and the efficiency of performance. If the latter remains constant, then any decrease in work will be associated with a decrease in expenditure of energy. We have shown that the output and hence, in all likelihood, the work of the heart are decreased by certain therapeutic procedures. It is probably justifiable to assume that the decrease in work is accompanied by a diminution in the energy expended by the heart. Other effective therapeutic measures do not decrease the cardiac work but may even increase it somewhat. However, it is probable that these measures increase the mechanical efficiency and thereby diminish the energy expended. If this is true, it would appear that all the therapeutic measures which are useful in treating congestive heart failure have one fundamental action in common—they tend to rest the heart.

The reasoning which has led to this conclusion rests on a number of assumptions. However, it is supported by strong evidence, which is as follows: It has been amply shown both clinically (Stewart and Cohn[13] and experimentally (Patterson, Piper and Starling[14]) that heart failure is associated with cardiac dilatation and that improvement is accompanied by diminution in the size of the heart. According to Starling and Visscher,[15] whose findings were confirmed by Hemmingway and Fee,[16] the energy expended by a heart is proportional to its diastolic volume, regardless of the work accomplished. If this law is applicable to man, then it is evident that any measure which produces a decrease in the degree of cardiac dilatation will reduce the energy expended by the heart (provided, of course, that it does not increase the pulse rate). Since practically all measures which produce clinical improvement do decrease the size of the heart, it may be assumed that they diminish its expenditure of energy. We believe that this is the chief effect of all the various therapeutic measures which are useful in the treatment of heart failure. They tend to rest an overstrained organ.

Congestive phenomena occurring in persons with concretio cordis are due to a mechanism which is different from that responsible for heart failure of the ordinary type. The thickened pericardium prevents

13. Stewart, H. J., and Cohn, A. E.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart: II. The Effect on the Output in Normal Human Hearts; Effect on Output of Hearts in Heart Failure with Congestion in Human Beings, J. Clin. Investigation **11**:917, 1932.

14. Patterson, S. W.; Piper, H., and Starling, E. H.: The Regulation of the Heart Beat, J. Physiol. **48**:465, 1914.

15. Starling, E. H., and Visscher, M. B.: Regulation of the Energy Output of the Heart, J. Physiol. **62**:243, 1922.

16. Hemmingway, A., and Fee, A. R.: Relationship of the Volume of the Heart and Its Oxygen Usage, J. Physiol. **63**:299, 1927.

filling and hence limits the energy which the heart can expend. Under such conditions the heart cannot dilate sufficiently to carry on the circulation adequately. Resection of the pericardium allows the heart to perform more work. In patients with obliterative pericarditis a condition of true cardiac insufficiency exists, for the heart is unable to expend sufficient energy. In the usual type of congestive failure the condition is rather that of cardiac inefficiency, for the heart can perform its work, but only at the price of a wasteful expenditure of energy.

SUMMARY

The cardiac output per minute of persons with congestive heart failure tends to be decreased by rest, venesection, morphine, thyroidectomy and abdominal paracentesis. In proportion to the metabolic needs the output may or may not be diminished by these procedures.

In patients with auricular fibrillation the restoration of the normal rhythm with quinidine has been associated with an increase in the cardiac output.

Resection of the pericardium of a patient with obliterative pericarditis was followed by an increase in the cardiac output.

The mechanism of improvement produced by the various therapeutic measures has been discussed. It is concluded that pericardial resection produces improvement in patients with concretio cordis by allowing the heart to do more work. On the other hand, therapeutic benefit in heart failure of the ordinary type is believed to be dependent on one fundamental factor: rest of the heart as a result of diminished expenditure of energy. Such an effect may be brought about either (*a*) by procedures which diminish the work done by the heart or (*b*) by measures which increase its mechanical efficiency so that less energy is wasted.

EFFECT OF HIGH INTRAPLEURAL PRESSURE ON BLOOD PRESSURE

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The purpose of the present paper is to report rather than to explain certain observations on the effects of increased intrapleural pressure on the blood pressure. The clinical picture resulting from an increase in pressure in the pleural cavity is sufficiently definite to be termed a syndrome, and although in my experience this syndrome has been observed commonly, it has only been hinted at in the literature and is generally unknown and unrecognized. I can best present its characteristics by reporting the cases which first called it to my attention.

REPORT OF CASES

Miss E. C. was seen in consultation with Dr. O'Neill at the Evanston Hospital on Aug. 4, 1931. Five days previously, in an automobile accident, she had suffered a severe injury to the right side of the thorax. A roentgenogram showed that five ribs on the right side were broken and that the right pleural cavity was filled with fluid and air. For the first few days the temperature was elevated to from 100 to 101 F. It then fell to 98 F., and at the same time the pulse rate rose from 110 to 120. When I first saw the patient she presented a picture characteristic of traumatic shock. There was marked pallor, the extremities were cold and the body was covered with beads of perspiration. The pulse rate was 120, and the respiratory rate was 26. Breathing was shallow and grunting. The pulse, which was extremely small, disappeared almost completely on inspiration.

The blood pressure on expiration was 102 systolic and 72 diastolic. During inspiration no reading could be obtained at any level. The pressure in the pleural cavity was + 28 cm. of water. After 525 cc. of pure blood was removed, the pressure in the pleural cavity was lowered to 11 cm., and a definite and dramatic change was produced in the patient's condition: The pallor disappeared, the extremities became warm, and the sweating stopped abruptly. The pulse increased in volume, and the rate fell to 100. The expiratory blood pressure rose to 112 systolic and 72 diastolic. The inspiratory systolic pressure was now 90. By the next day the original symptoms and signs had returned. The expiratory blood pressure was 84 systolic and 60 diastolic. There was no inspiratory pressure. The pressure in the pleural cavity was + 12 cm. of water. After the removal of 900 cc. of blood, air was injected into the pleural cavity until the pressure was + 8. The picture was again reversed; the blood pressure was then 112 systolic and 65 diastolic.

A similar picture was presented by a patient seen in consultation with Dr. Keaton and Dr. Mussil at the St. Francis Hospital (Evanston). A man, 28 years old, had had spontaneous pneumothorax complicated by spontaneous hemorrhage into the pleural cavity. I saw him a week after the onset. Pallor, diaphoresis and coldness of the extremities were marked. The pulse rate was 120, and the respiratory

rate, 30 per minute. The expiratory blood pressure was 110 systolic and 90 diastolic. There was no inspiratory pressure. The pressure in the pleural cavity was + 30 cm. of water. The withdrawal of 1,500 cc. of practically pure blood lowered the pressure to + 4 cm. The pallor disappeared, and the sweating stopped immediately. The pulse rate fell to 110. The systolic blood pressure rose to 120, and the diastolic pressure fell to 80. There was still a difference between the inspiratory and the expiratory pressure, but it was less marked than before the aspiration.

In both of these cases there was a combination of hemorrhage and of high pressure in the pleural cavity. In both there was a definite lowering of the blood pressure with a marked fall during inspiration. While the expiratory blood pressure was well above that usually productive of signs and symptoms of circulatory failure (shock), definite shock was present. The mean blood pressure evidently was below the critical level. In both cases lowering the intrapleural pressure by aspi-

TABLE 1.—*Effects of Changes in Intrapleural Pressure*

	Intrapleural Pressure, Cm. of Water		Systolic Pressure, Mm. of Mercury		Diastolic Pressure, Mm. of Mercury
	Inspiratory	Expiratory	Expiratory	Inspiratory	
Mr. J. (right pneumothorax)					
Before injection	−6	−2	130	130	90
After injection of 800 cc. of air	−1	+2	155	130	90
Mr. W. (left pneumothorax)					
Before injection	−2	+8	140	120	80
500 cc. of air removed	−8	−0	120	120	80
500 cc. of air injected	−2	+8	120	120	80
One hour later	−2	+8	140	120	80
Mrs. G. (left pneumothorax)					
Before injection	−2	+6	145	120	85
500 cc. of air removed	−8	−1	120	120	80
500 cc. of air injected	−2	+6	140	120	85

rating fluid raised the blood pressure, decreased the discrepancy between its inspiratory and expiratory phases and brought about the immediate disappearance of the symptoms of circulatory collapse.

I have since observed this discrepancy between the inspiratory and the expiratory blood pressure in patients with pleurisy with effusion and with both spontaneous and artificial pneumothorax. It occurs only when the pressure in the pleural cavity is positive. In some cases the mean blood pressure is raised; in others, lowered. A serious drop occurs only when the intrapleural pressure is very high or there is some complicating factor, such as hemorrhage. One is usually able to detect the variation by palpating the radial artery, and in extreme cases complete absence of pulsation during inspiration is occasionally noted. The phenomenon is produced by compression of either the right or the left lung. If the breath is held on inspiration, the blood pressure gradually rises and comes through at a higher level, but only after considerable delay.

Table 1 shows the effects of raising and of lowering the intrapleural pressure in different patients with artificial pneumothorax. I did not feel justified in producing extremely high pressures for purely experimental purposes.

The observations and syndrome reported are of frequent occurrence and of real importance. In cases of pleurisy with effusion and of spontaneous and artificial pneumothorax the fall in the blood pressure on inspiration indicates definite cardiorespiratory embarrassment, and a lowering of the blood pressure on expiration points to a condition which may lead rapidly to circulatory failure and death. It is important to know that even when there is an expiratory pressure of over 100 mm. of mercury, the mean pressure may be below the critical level for shock. In cases of hemorrhage into the pleural cavity it is important to know that both the loss of blood and the rising intrapleural pressure tend to lower the blood pressure and that the collapse incident to it may be immediately relieved by reducing the pressure in the pleural cavity.

I have been able to find but one clinical reference to this exaggerated variation in the volume of the pulse in cases of increased intrapleural pressure: Rosenbach [1] in 1886 noted an inspiratory weakening or disappearance of the radial pulse in cases of massive pleural effusion. He suggested that it was caused by the closure of the vena cava by the contraction of the diaphragm. That his surmise was incorrect is shown by the fact that in one of my cases the diaphragm had been paralyzed. Many other writers have noted a weak, rapid and irregular pulse. Two other observations which bear directly on the cases reported and which can therefore best be mentioned at this point are as follows: In Starling's [2] textbook on physiology it is stated that acute hemorrhage frequently produces a marked exaggeration of the Traube-Hering waves, and Frantzel [3] noted clinically that when there is an increase in the intrapleural pressure the blood pressure rarely falls unless there are complicating factors.

The physiologic problems involved are numerous and intricate and are concerned with the whole field of respiration and circulation and the mechanical and the reflex factors which influence them.

Changes in blood pressure synchronous with the phases of respiration are normal. Known generally as the Traube-Hering waves, they have been the subject of numerous and extensive investigations. The

1. Rosenbach, O.: Virchows Arch. f. path. Anat. **105**:215, 1886.

2. Starling, E. H.: Principles of Human Physiology, ed. 6, Philadelphia, Lea & Febiger, 1933.

3. Frantzel, cited by Lieven, P.: Ueber den Blutdruck bei den verschiedenen Formen des Pneumothorax, Dorpat, H. Laakmann, 1893.

literature on the subject has been thoroughly reviewed by Tigerstedt.[4] On inspiration there is a primary fall and a secondary rise of blood pressure, and on expiration, a primary rise and a secondary fall. The secondary rise on inspiration and the fall on expiration become apparent only if respiration is slow, and both signs are absent if the pericardial sac is open to atmospheric pressure. This indicates that the secondary changes are caused by variations in the pressure on the heart and on the intrathoracic vessels.

There are two possible explanations of the Traube-Hering phenomenon, the one mechanical and the other reflex. Tigerstedt listed all the factors concerned, as shown in table 2.

The mechanical explanation is the simplest and most tempting, but experimental evidence suggests that it is less important than the reflex explanation. It is easy to argue that at the beginning of inspiration

TABLE 2.—*Factors Concerned with the Traube-Hering Phenomenon*

	Inspiration	Expiration
1. Suction of blood toward the heart	Increased	Decreased
2. Diastole of heart	Easier	Harder
3. Systole of heart	Harder	Easier
4. Diameter of pulmonary vessels	Increased	Decreased
5. At change to the other phase of respiration, blood remains in vessels of lung or is forced out of them	Remains back	Forced out
6. During this phase of respiration the blood flow through the pulmonary vessel is	Easier	Harder
7. Then as a result of factors 4 and 6 the blood flow to the left heart is	First decreased, then increased	First increased, then decreased
8. The pulse rate with the vagus nerves intact	Increased	Decreased
9. The vessels of the systemic circulation are	Wider	Narrower
10. The pressure in the abdominal cavity is	Increased	Decreased

the rapid increase in the size of the pulmonary bed causes a temporary delay of blood flow to the left heart and a fall in resistance in the pulmonary circuit but the increased aspiration of blood to the right heart acts eventually in the reverse direction, and that on expiration the increased intrathoracic pressure forces blood from the lung to the left heart and so raises the pressure temporarily, the later fall being caused by the increased resistance in the pulmonary circuit and by the interference with venous return to the right heart and the resulting decreased supply of blood to the left heart.

These factors probably operate increasingly under the abnormal condition of pulmonary collapse and high intrapleural pressure. They might have been accepted as the sole explanation had not Fredericq [5]

4. Tigerstedt, R.: Die Physiologie des Kreislaufes, ed. 3, Berlin, W. de Gruyter & Co., 1923, p. 1.

5. Fredericq, cited by Tigerstedt.[4]

shown that the changes in blood pressure synchronous with respiration are independent of mechanical factors, persisting in the curarized animal with both pleural cavities widely opened. This suggested that they are caused by changes in the tone of the vasoconstrictor center produced by rhythmic variations in the oxygen and carbon dioxide content of the blood. Against this explanation is the work of Plumier,[6] who found that the waves disappear after section of the nerves at the root of the lung.

In the normal human being the waves are not ordinarily observable. Frost,[7] however, has shown that on deep inspiration that is held the pressure first rises a little, then falls abruptly and then rises and that on deep expiration these effects are reversed. Their noted increase in cases of increased pressure in the pleural cavity may be the result of mechanical factors, of poor aeration of the blood and of resulting changes in vasoconstriction, or of reflexes arising in the lung and acting on the vasoconstrictor center. It is my feeling that in this condition the former factors are of chief importance, namely, the great hindrance to the return of blood to the right heart and the marked changes in resistance in the pulmonary circuit.

There have been numerous clinical studies on the effect of artificial pneumothorax on the blood pressure, and both the results within the different series and the results of the different observers have been inconstant. In some patients there is a temporary rise in blood pressure, in others a fall and in others no change. Practically all investigators have agreed that with the pressures used the changes are unimportant and transitory, disappearing in the course of an hour or two. Steidl and Heise [8] in most patients found a fall of systolic pressure of from 7 to 40 mm. of mercury as a result of simply passing the needle through the pleura. After injections of air Burstein [9] found an average rise of pressure of 12.4 mm. of mercury. Bendove [10] found an increase of pressure in eight of fourteen cases, no change in four and a fall in two. All the readings returned to normal in an hour. Vazzoler [11] found a constant decrease in the pulse pressure caused chiefly by a rise of from

6. Plumier, cited by Tigerstedt.[4]

7. Frost, H. M., in New England Mutual Life Insurance Company: Life-Insurance Medicine, Boston, 1926, vol. 1, p. 136.

8. Steidl, J., and Heise, F. H.: The Pulse-Rate and Blood-Pressure During Artificial-Pneumothorax Insufflations, Am. Rev. Tuberc. **26**:730, 1932.

9. Burstein, M. A.: Der Einfluss des künstlichen Pneumothorax auf den Blutdruck bei Tuberkulösen, Ztschr. f. Tuberk. **21**:138, 1913-1914.

10. Bendove, R. A.: The Circulatory Changes in Artificial Pneumothorax, Am. Rev. Tuberc. **12**:107, 1925.

11. Vazzoler, G.: Di alcuni effetti sul circolo del pneumotorace terapeutico, Folia med. **14**:502, 1928.

5 to 15 mm. of mercury in the diastolic level. Klukowski [12] found that it fell in 78 per cent, was unchanged in 14 per cent and rose in 8 per cent. The pulse rate was slowed in 65 per cent, unchanged in 13 per cent and increased in 22 per cent.

Bruns,[13] Weil and Sackur,[14] Rist and Carpi,[15] Bernard and Robert [16] and Parisot and Hermann [17] agreed that in experimental animals artificial pneumothorax as used clinically causes no important or lasting change in the blood pressure. Parisot and Hermann noted a slowing of the pulse, which has also been observed by Sauerbruch [18] and Walther,[19] the latter having found that it does not occur if the vagus nerves are cut.

Knoll,[20] Rosenbach, Lieven,[3] Walther, Dunn [21] and others have studied experimentally the effects of higher pressures in the pleural cavity. Knoll found that there was no change in the blood pressure if the pressure in the pleural cavity or pericardium was raised gradually to atmospheric pressure. If it was raised rapidly above that level, there occurred first a rise in blood pressure and then an abrupt fall, which, unless the pressure was relieved, led rapidly to death. As the pressure was raised, the systemic veins became progressively engorged. After decompression the blood pressure rose far above normal, and that was interpreted as being caused by the sudden release of the intrathoracic dam and the flooding in of the blood held back in the veins.

Rosenbach, Lieven and Walther made similar observations. All of them interpreted the primary rise in blood pressure as being due to a compensating vasoconstriction. The fall in blood pressure came just before death and was abrupt. They expressed the opinion that the fall was caused by interference with the return of the venous blood by pressure on the great veins and on the right heart. Walther and Sauer-

12. Klukowski, J.: L'influence du pneumothorax artificiel sur la tension artérielle, J. de méd. et chir. prat. **103**:331, 1932.

13. Bruns, O.: Ueber Folgezustände des einseitigen Pneumothorax, Beitr. z. Klin. d. Tuberk. **12**:1, 1909; Ueber die praktische Bedeutung der Zirkulationsänderung durch einseitigen Lungenkollaps bei therapeutischen Eingriffen an der Lunge, ibid. **29**:253, 1913.

14. Weil and Sackur, cited by Steidl and Heise.[8]

15. Rist and Carpi, cited by Steidl and Heise.[8]

16. Bernard and Robert, cited by Steidl and Heise.[8]

17. Parisot, J., and Hermann, H.: Action sur l'appareil cardiovasculaire du pneumothorax artificiel experimental, Compt. rend. Soc. de biol. **135**:1034, 1922.

18. Sauerbruch, E. F.: Die Chirurgie der Brustorgane, ed. 2, Berlin, Julius Springer, 1920, vol. 1, p. 608; vol. 2, p. 718.

19. Walther, H. S.: Deutsches Arch. f. klin. Med. **119**:253, 1912.

20. Knoll: Schmidt's Jahrb. **146**:179, 1882.

21. Dunn, J. S.: The Effect of Experimental Pleural Effusion on the Blood Pressure in the Right Ventricle, Quart. J. Med. **13**:57, 1919.

bruch stressed the initial slowing of the pulse caused by stimulation of the vagus nerve. Rosenbach was the only one who noted or reported an increase in the Traube-Hering waves.

The effects of increased pressure in the pericardium bear a direct relation to the present problem. It has been frequently shown that those effects are caused purely by interference with the return of venous blood. In experiments performed in 1923 Claude Beck and I found a marked rise in the venous pressure. There was an initial rise in the blood pressure, but as the venous pressure reached a maximum and the intrapericardial pressure approached it, the blood pressure began to fall. The fall was gradual, not abrupt and rapidly fatal, as in cases of high pressure in the pleural cavity; and it could be maintained at any desired level by regulating the pressure in the pericardium. Section of the vagus nerves and avulsion of the stellate ganglions did not alter the picture. Beck and Isaac [22] reported a decrease in the output of the heart which was not reflected in the blood pressure until it had become extreme.

When the pressure in the pleural cavity is raised, there are the same factors to be considered, but the condition is much less simple. There is also collapse of one lung and partial collapse of the other. There are displacement of the heart and mediastinum, a reduction in the vital capacity and a change in the blood flow through the lungs and in the pressure in the pulmonary circulation. All of those factors must be considered as contributing to the syndrome.

The older clinicians, Trousseau,[23] Bartels,[24] Leichtenstern,[25] Rosenbach and others, expressed the opinion that cardiac failure in cases of massive pleural effusion is purely a matter of displacement of the heart and torsion of the great vessels. Bartels in particular was responsible for the idea that kinking and occlusions of the vena cava account for the sudden death that occasionally occurs. That theory was upset by the demonstration at postmortem examination that those deaths are caused by embolism of the pulmonary artery, the thrombi having formed in the right auricle and ventricle. Extreme displacement of the heart by pulmonary fibrosis occasionally causes tachycardia and dyspnea, but is usually well tolerated; the simple displacement is probably a minor factor. Bruns, and Dock and Harrison [26] have shown that there is a

22. Beck, Claude, and Isaac, L.: Pneumocardiac Tamponade, J. Thoracic Surg. **1**:124, 1931.

23. Trousseau, cited by Sauerbruch.[18]

24. Bartels, cited by Sauerbruch.[18]

25. Leichtenstern, O., in Gerhardt, C.: Lehrbuch der Kinderkrankheiten, ed. 5, Tübingen, H. Laupp, 1897-1899.

26. Dock, W., and Harrison, T. R.: The Blood Flow Through the Lungs in Experimental Pneumothorax, Am. Rev. Tuberc. **10**:534, 1925.

decreased flow of blood through a collapsed lung. Richards, Riley and Hiscock [27] found an appreciable reduction in the output of the heart during artificial pneumothorax. With high pressures Dunn observed a rise in pressure in the right ventricle, and it has been noted that it falls abruptly shortly before the fall in systemic pressure. Schlaepfer [28] found that ligating one pulmonary artery causes a rise in pressure in the opposite artery, and Horine and Warner [28] have recently shown that ligation of one pulmonary artery causes a transient fall in the systemic pressure, which disappears in thirty seconds, but if the vasomotor center is thrown out by section of the cervical portion of the spinal cord, the pressure continues to fall, and the dog dies. Bendove noted an increase in the pulmonary second sound and in the transverse diameter of the heart in patients who responded to artificial pneumothorax with a rise in blood pressure.

CONCLUSION

It can be said, therefore, that high pressure in the pleural cavity acts directly on both the pulmonary and the systemic circulation: on the former by collapsing the lung and on the latter by compressing the great veins.

Collapse of the lung causes: (1) a decrease in the flow of blood through the collapsed lung, (2) a rise in pressure in the pulmonary circulation, (3) an increased strain on the right heart and (4) a reduction in the vital capacity.

Compression of the great veins causes: (1) a rise in the venous pressure, (2) an insufficiency in the return of venous blood and (3) a decreased output of the heart.

Up to relatively extreme degrees of pressure these hindrances are compensated for by an increase in tone of the vasoconstrictor center. The first sign of the strain on this compensatory mechanism is an exaggeration of the Traube-Hering waves, a tendency for the peripheral resistance to give way during inspiration. A time comes when the center can no longer fully compensate, and the mean blood pressure falls below the critical level.

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27. Richards, D. W., Jr.; Riley, C. B., and Hiscock, M.: Cardiac Output Following Artificial Pneumothorax in Man, Arch. Int. Med. **49**:994 (June) 1932.

28. Schlaepfer, cited by Horine, C. F., and Warner, C. G.: Experimental Occlusion of the Pulmonary Artery: Anatomic Study, Arch. Surg. **28**:139 (Jan.) 1934.

ACUTE GLOMERULONEPHRITIS FOLLOWING PNEUMOCOCCIC LOBAR PNEUMONIA

ANALYSIS OF SEVEN CASES

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Twenty years ago Volhard and Fahr [1] stated that the streptococcus played the most important rôle in the various types of nephritis and that the pneumococcus was the next most important infectious agent. Rake [2] recently reviewed the literature concerning the importance of the pneumococcus in the etiology of nephritis and called attention to the fact that whereas the streptococcus has recently received the chief attention, numerous papers appearing in the last decade of the nineteenth century dealt with the significance of pneumococcic infection as an inciting agent in acute nephritis. The recent comprehensive clinical and experimental studies of Blackman and his associates [3] produced renewed interest in the problem. These authors noted pathologic evidence of acute nephritis in 9.4 per cent of 95 young children who died of the various types of pneumococcic infection. "Outspoken examples of acute nephritis were found only in infants with pneumococcal infections, usually of long duration, other than pneumonia alone. It was not present in the kidneys of the adults studied who had similar, chronic pneumococcal infection."

This study consists of a clinical analysis of 7 cases of acute glomerulonephritis following pneumococcic lobar pneumonia which occurred in 1,004 instances of the latter condition seen at the Presbyterian Hospital between 1918 and 1933. All the cases were diagnosed clinically. Postmortem studies were not made on the 2 patients who died.

Only the cases diagnosed as instances of pneumococcic lobar pneumonia and acute nephritis were included in this report. It is believed that a number of cases of acute nephritis following lobar pneumonia were overlooked, since the failure to carry out comprehensive laboratory studies may have prevented the diagnosis of this disease. Three cases of acute nephritis following lobar pneumonia in which typing

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital.

1. Volhard, F., and Fahr, K. T.: Die Brightsche Nierenkrankheit, Berlin, Julius Springer, 1914.

2. Rake, G.: Guy's Hosp. Rep. **83**:430, 1933.

3. (*a*) Blackman, S. S.; Brown, J. H., and Rake, G.: Bull. Johns Hopkins Hosp. **48**:74, 1931. (*b*) Blackman, S. S., and Rake, G.: ibid. **51**:217, 1932. (*c*) Blackman, S. S.: ibid. **55**:1, 1934; (*d*) ibid. **55**:85, 1934.

of the sputum was unsatisfactory were excluded from this study. Two cases of acute glomerulonephritis in children which seemed to be associated with pneumococcic infection were eliminated from the series because of inadequate laboratory studies.

ANALYSIS OF CASES

The table presents in outline the analysis of the histories of the 7 patients with acute glomerulonephritis associated with pneumococcic lobar pneumonia. The following data were selected for study:

Age.—One patient was in the second decade of life, 2 in the third, 3 in the fourth and 1 in the fifth.

Sex.—Five of the patients were men, and 2 were women. In a study[4] of 381 cases of acute glomerulonephritis in which the chief preexisting infectious agent was the hemolytic streptococcus, it was found that the disease developed twice as frequently in men as in women.

Past History of Nephritis.—None of the 7 patients gave a past history of symptoms or signs indicative of preexisting nephritis.

Culture of the Sputum.—The cultures obtained from the sputum showed pneumococcus type I in 4 patients, pneumococcus type II in 1 and pneumococcus type III in 2.

Culture of the Blood.—In 5 of the patients the blood culture was negative throughout the course of the pneumonia. In 1 of the patients who died a type I pneumococcus was revealed in the blood on three occasions early in the course of the pneumonia. After specific serum therapy the blood culture became negative. In the second patient a type III pneumococcus was observed repeatedly in the blood before death. No cardiac murmurs or embolic phenomena were noted in this patient.

Complications.—Three of the patients had no complications. One of the patients presented the signs of mitral stenosis without evidence of active rheumatic fever or cardiac insufficiency. In 1 case serum disease appeared. In another instance of serum disease otitis media and mastoiditis were found to be caused by the pneumococcus. Pericarditis was the complication in the seventh case.

Interval in Days Between the Onset of Pneumonia and the Probable Onset of Nephritis.—While it was possible to determine with reasonable accuracy the day of onset of the pneumonia, it was difficult to judge the exact day of onset of the acute nephritis, since urinalyses were made as a routine only at weekly intervals and the problem of renal complication was not generally considered by the attending physician until the appearance of a dramatic sign or symptom of the disease.

4. Seegal, D.; Seegal, B. C., and Lyttle, J. D.: Unpublished observations.

Name	Age, Years	Sex	Past History of Nephritis	Pneumococcus in Culture of the Sputum	Blood Culture	Complications	Interval Between Onset of Pneumonia and Probable Onset of Nephritis, Days	Examination of Urine During Pneumonia and Prior to Probable Onset of Nephritis: Albumin	Sediment	Examination of Urine After Onset of Nephritis: Albumin	Sediment
C. D.	24	M	Negative	Type II	Negative	None	±20	VFT VFT VFT	Negative Negative Negative	VHT	Few red cells; many hyaline and granular casts; few cellular casts
J. H.	38	M	Negative	Type I	Negative	None except serum disease	±20	FT FT T	Negative Negative Negative	HT	Many hyaline and granular casts; many red cells
J. F.	35	M	Negative	Type III	Positive 3 times during course	Pericarditis	±21	No data		HT	Many casts; many red cells
A. S.	28	F	Negative	Type I	Positive 3 times early in course	Otitis media due to pneumococcus type I; mastoiditis due to pneumococcus type I; serum disease	±16	FT VFT FT	Occasional red cells (patient menstruating) Negative Negative	HT	Occasional cellular casts; many red cells
T. L.	49	M	Negative	Type I	Negative	None	±21	FT FT VFT None	Many granular casts Occasional white blood cells Moderate number of white cells Few casts	T	Many casts of all kinds; many red cells
J. L.	16	M	Negative	Type I	Negative	None	±14	FT T T	Negative Negative Few casts	HT	Many casts; urine loaded with red cells, smoky
G. R.	38	F	Negative	Type III	Negative	None except inactive rheumatic cardiac disease with mitral stenosis	±19	FT FT FT	Negative Negative Negative	HT	Many casts; many red cells

* VFT indicates a very faint trace of albumin; FT, a faint trace; T, a trace; VHT, a very heavy trace; and HT, a heavy trace.

*Following Pneumococcic Lobar Pneumonia**

Blood Urea, Mg.	Phenolsulphonphthalein Test, Percentage Excreted	Blood Pressure		Examination of Eyegrounds	Edema	Decrease in Red Cell Count During Nephritis	Treatment with Specific Serums	Serum Sickness	Comment
		Systolic	Diastolic						
4.34 2.82 0.62 0.29	15 40 56	105 120	48 58	Few fresh hemorrhages	Moderate	2,500,000	Not given	None	Patient followed in outpatient department for 2 months, during which he continued to show a heavy trace of albumin and normal blood pressure; no further observations
0.53 0.35	42	120	80	Normal	None	1,200,000	Given	Present	No data available after discharge
1.13 1.27	No test made	130	70	Normal	None	No data	Not given	None	Previous attack of pneumonia 1 month before present bout; patient well for 10 days, when second attack occurred, which led to death
2.31 2.08 2.66 2.70 3.10 3.30	45 early in course of nephritis	102 116 125 140	65 66 75 70	Not made	Marked	1,800,000	Given	Present	Patient died of uremia 1 month after onset of nephritis; 1 culture made from throat showed hemolytic Staph. aureus
1.28	15 early; 50 at discharge from hospital	130 155 100	65 90 60	Not made	Slight	1,600,000	Not given	None	Healing in 1 year, when blood pressure was 116 systolic and 75 diastolic and 140 systolic and 80 diastolic, and urinalysis twice gave negative results; scarlet fever without complications in childhood
1.60 1.20 0.26	50 30 35 25 30 40 50 60 65	110 130	65 90	Normal	None	1,400,000	Not given	None	Healing in 14 months; repeated negative results of urinalyses for next 9 years
1.31 0.89 0.52 0.27	52	96 100 116 115 120	70 50 64 78 80	Normal	None	1,200,000	Not given	None	Healing in 7 months

Nevertheless, it was possible to gain an approximate idea of the day of onset of nephritis. The table shows that an interval of from fourteen to twenty-one days intervened between the onset of pneumonia and that of acute nephritis. In 4 of the cases there was an afebrile period of three, four, six and seven days, respectively, prior to the recognized onset of renal inflammation. It appears that the "silent period" observed in cases of postscarlatinal nephritis is also present in this group of cases of nephritis after pneumococcic lobar pneumonia.

Examination of the Urine During Pneumonia and Prior to the Probable Onset of Nephritis.—The table shows that urinalyses during pneumonia and prior to the probable onset of nephritis revealed small amounts of albumin and nothing of significance in the sediment, except in one or two determinations in which casts were observed. Gross hematuria and microscopic evidence of red cells in the sediment were not noted except in the case of A. S., who was menstruating at the time of admission. Two of the subsequent urinalyses in this case prior to the onset of nephritis showed nothing of significance in the sediment.

Examination of the Urine After the Onset of Nephritis.—Urinalyses at the onset of nephritis gave characteristic results, and hematuria was a dominant feature. Albuminuria was marked, and all the types of casts usually associated with the diagnosis of acute nephritis were repeatedly observed. Neale[5] analyzed the results of urinalysis in 287 cases of lobar pneumonia in adults and noted that in 3.4 per cent albuminuria, cylindruria and microscopic hematuria were shown between the third and the tenth day after the onset of the disease.

Blood Urea.—Retention of nitrogen occurred in all 7 cases.

Phenolsulphonphthalein Test.—Three of the patients showed marked diminution in their ability to excrete phenolsulphonphthalein during the early stages of nephritis, but in all these persons the results of the phenolsulphonphthalein test were normal on the patient's discharge from the hospital. All the remaining patients on whom the test was performed showed no evidence of retention of the dye.

Blood Pressure.—A striking feature in this series of cases was the absence of significant hypertension, particularly in the diastolic phase. None of the patients showed a diastolic blood pressure of over 90, and in 5 of the 7 cases the diastolic blood pressure never exceeded 80. One patient, aged 49, had a systolic blood pressure of 155 on one occasion. The two other readings in this case were 130 and 100. Another patient had a systolic blood pressure of 140, but three other readings were 102, 110 and 125. With these two exceptions, the systolic blood pressure was never found to exceed 130.

5. Neale, A. V.: Brit. M. J. **2**:891 (Nov. 17) 1928.

It was surprising to find such a striking absence of hypertension in a group of 7 patients with acute nephritis, in whom the results of urinalysis and the values for blood urea were so abnormal.

Examination of the Eyegrounds.—Examination of the eyegrounds was made in 5 of the 7 cases. No findings were revealed indicative of preexisting damage. In one case a few fresh hemorrhages observed during the acute stage of the nephritis disappeared later.

Edema.—In 4 of the patients demonstrable subcutaneous edema failed to develop. In 1 case there was slight, in a second moderate, and in a third marked, edema.

Decrease in Red Blood Cell Count During the Nephritis.—In the 6 patients for whom adequate data were available, the decrease in the red blood cell count during the course of the nephritis was striking. The table shows that the highest reduction in the count was 2,500,000 and the lowest 1,200,000.

Treatment with Specific Serums.—Two of the patients with type I pneumococcic infection received antipneumococcus horse serum. Serum sickness developed in both, and 1 patient died of uremia. The nephritis which occurred in these cases could not be confused with the renal changes of serum sickness which have been described by Rackemann, Longcope and Peters.[6]

Course of the Nephritis.—In 1 of the 2 patients who died terminal uremia developed one month after the onset of nephritis. The cause of the death of the second patient was considered to be pneumococcic septicemia complicated by pericarditis. There was no clinical evidence of bacterial endocarditis. The nephritis was not considered the cause of death but may have contributed to it. Three of the patients were carefully observed subsequently and the lesions were considered healed in from seven to fourteen months after the onset of renal inflammation. The sixth patient was observed for two months and continued to show severe albuminuria and a normal blood pressure. His further history is unknown. The seventh patient could not be adequately studied after his discharge.

COMMENT

Analysis of the histories in the 7 cases included in this study shows that a typical picture of acute glomerulonephritis followed pneumococcic lobar pneumonia. The clinical features characteristic of the nephritis are outlined in the table. The histories in these cases in adults may be offered as further evidence that the pneumococcus or its products are

6. Rackemann, F. M.; Longcope, W. T., and Peters, J. P.: The Excretion of Chlorids and Water and the Renal Function in Serum Disease, Arch. Int. Med. **18**:496 (Oct.) 1916.

capable of inducing acute glomerulonephritis. This group of cases may be classified with those of infants with clinical histories of acute nephritis following pneumococcic infection which were described by Blackman and Rake.[3b]

The histories of the 7 patients and the data obtained from laboratory examinations were carefully studied to determine the presence of infections other than those caused by the pneumococcus. Such concomitant infections were absent. In 1 case a culture made as a routine of material from a normal-appearing throat showed hemolytic Staphylococcus aureus but no hemolytic streptococcus. In a second case, that of a patient who never manifested symptoms or signs of pharyngitis, cultures of material from the throat made on the second and on the eighteenth day of the nephritis showed no hemolytic streptococcus. On the thirtieth day, when the nephritis was subsiding, a culture of material from the throat showed alpha prime (not beta) hemolytic streptococcus. Results of determinations of antistreptolysin made on the serum of this patient were within normal limits. Similar determinations carried out on the serum of another patient with nephritis following lobar pneumonia also gave normal values. The last-mentioned case has been excluded from this series, since the typing of the sputum was unsatisfactory. Studies [7] of the antistreptolysin titer of patients with acute nephritis following infection with the hemolytic streptococcus showed values higher than normal in the great majority of the cases. Although it is impossible to exclude the possibility of a concomitant infection due to the hemolytic streptococcus in these cases of lobar pneumonia which were followed by acute glomerulonephritis, the accurate clinical observations lend little credence to this possibility.

During the period in which this series of cases was studied there were 1,004 cases of pneumococcic lobar pneumonia at the Presbyterian Hospital. The incidence of acute nephritis following lobar pneumonia at this hospital is, therefore, about 0.7 per cent. This value would probably be higher if opportunity had been available to study all the cases of lobar pneumonia more carefully.

The incidence of nephritis following scarlet fever is considered to be in the neighborhood of from 1 to 2 per cent. Recently, Lucchesi and Bowman [8] found nephritis a complication in only 1.26 per cent of 5,377 cases of scarlet fever. It is surprising to note how closely the frequency for nephritis following pneumococcic lobar pneumonia approaches this value. Since the total number of infections due to the hemolytic streptococcus in New York City is far greater than the

7. Seegal, D., and Lyttle, J. D.: Proc. Soc. Exper. Biol. & Med. **31**:211, 1933; unpublished observations.

8. Lucchesi, P. F., and Bowman, J. E.: Antitoxins Versus No Antitoxin in Scarlet Fever, J. A. M. A. **103**:1049 (Oct. 6) 1934.

number due to the pneumococcic infections, it seems only reasonable to assume that in the great majority of cases acute nephritis is due to the former organism.

CONCLUSIONS

An analysis has been made of the histories of 7 patients with acute glomerulonephritis following pneumococcic lobar pneumonia.

The nature of the data obtained from the laboratory and certain points in the clinical history have been shown in tabular form and commented on.

The nephritis develops in from two to three weeks after the onset of the pneumonia and is characterized by severe albuminuria, hematuria, moderate to marked retention of nitrogen, striking reduction in the red cell count, slight to marked edema in one-half the cases and absence of significant hypertension.

Evidence of a concomitant infection due to the hemolytic streptococcus is not found in the clinical history.

The incidence of acute glomerulonephritis following pneumococcic lobar pneumonia in 1,004 cases was 0.7 per cent. This value closely approximates that for the incidence of nephritis following scarlet fever.

RELATIONSHIP OF PELLAGROUS DERMATITIS TO SUNLIGHT

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In the early descriptions observers expressed the belief that pellagra was caused by the sun, and it was accordingly designated by many writers as *mal de la sol* or sickness of the sun.[1] Since that time various writers have held that sunlight was either the sole cause or a major factor in the pathogenesis of the disease. Bass,[2] Ormsby,[3] Sutton [4] and Ruffin and Smith [5] described the development of pellagrous erythema in pellagrins exposed to direct sunlight. Some writers believed that the pellagra-producing portion of the sunlight is present in the violet end of the spectrum.[6] All these conclusions have, of necessity, been based on personal interpretations, at times without full regard for the inherent difficulties in distinguishing between the erythema of sunburn and that of pellagra.

The present study is concerned with observations on pellagrous dermatitis and the relationship of these cutaneous changes to exposure to sunlight.

METHODS AND OBSERVATIONS

During the past three and a half years thirty patients with pellagra and two normal persons were studied at the Lakeside Hospital in the following manner:

1. Ten pellagrins were exposed to large doses of ultraviolet radiation at a distance of 20 inches (53.34 cm.) while they were restricted to a diet of 2,900 calories, low in the pellagra-preventive substances. Each of the ten patients received daily increasing doses of radiation from a quartz mercury vapor arc lamp

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From the H. K. Cushing Laboratory of Experimental Medicine, Department of Medicine, Western Reserve University, and the Medical Service, Lakeside Hospital.

1. Roberts, S. R.: Pellagra, St. Louis, C. V. Mosby Company, 1912, p. 133.
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3. Ormsby, O. S.: A Practical Treatise on Diseases of the Skin, ed. 4, Philadelphia, Lea & Febiger, 1934, p. 417.
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for a period from four to forty minutes over a characteristic pellagrous lesion and also over another area of normal-appearing skin. In every instance the corresponding anatomic area on the opposite side of the body was protected from irradiation and served as a control.

The patch of normal-appearing skin of the ten pellagrins became increasingly pigmented after irradiation, but the area was not unlike the similarly exposed skin of the normal subjects. In no instance could the induced pigmentary changes be diagnosed as pellagrous, although the irradiated areas were well demarcated and passed through the stages of erythema, darkening and desquamation. Likewise, exposure of the pellagrous lesions to ultraviolet radiation was followed by additional pigmentary change, but irradiation did not prevent the dermatitis from healing.

Fig. 1.—Increased pigmentation of the antecubital fossa of a normal person and of a pellagrin after identical exposure to sunlight. The areas may be compared with the area of pellagrous dermatitis on the wrist of the pellagrin.

2. In eight other patients on the same diet low in pellagra-protective substances the area of pellagrous dermatitis was exposed to direct sunlight in increasing doses, ranging from twenty to sixty minutes each day, for a period of from seven to twenty days. In six of the eight patients also areas of normal-appearing skin were exposed to sunlight for the same intervals of time. In all the patients ipsilateral portions of the body were protected from sunlight.

The exposed areas of normal-appearing skin reddened at first, often became swollen and later desquamated and became pigmented, but none of them could be diagnosed as pellagrous. The exposure of the pellagrous lesion itself to sunlight was followed by somewhat similar changes, but the exposure did not prevent healing of the underlying pellagrous dermatitis.

3. In order to compare the effects of sunlight on the normal-appearing skin of pellagrins and on the skin of normal persons, two pellagrins and two normal persons with a similar degree of pigmentation were exposed to the sun in an identical manner. During the study the normal subjects received a generous diet high in calories and in nutritive value, and the pellagrins were restricted to one low in pellagra-preventive substances. Each person was exposed for one hour each day for five consecutive days.

The exposed skin of the normal subjects and of the pellagrins became reddened and swollen with subsequent desquamation (fig. 1), but little if any evidence could

Fig. 2.—A well demarcated lesion of pellagrous dermatitis which developed in the absence of direct sunlight.

be obtained of difference in the intensity or character of the response of the skin.

No pellagrin in the studies just outlined had a general relapse of the disease. Each patient ingested the full 2,900 calorie allowance of food and did not show additional signs or symptoms of pellagra, such as glossitis, dermatitis, stomatitis, diarrhea, vomiting or psychic changes.

4. To determine whether or not in potential pellagrins dermal changes could develop in the absence of direct sunlight, four adult volunteers, who had had numerous previous attacks of pellagra but were free from lesions at the time, were

offered a deficient diet. They were not urged to eat the food, however, since it was thought that they would eat less and less and that the disease would soon develop. Each patient was given 20 cc. of castor oil three times a day with the hope that excessive purgation might also aid in producing the disease. These volunteers were kept in the hospital away from direct sunlight throughout the course of the experiment.

Fig. 3.—Bilaterally placed, well demarcated areas of pellagrous dermatitis which appeared without exposure to direct sunlight.

Each patient ate less and less and consequently lost considerable weight by the end of the first month. Within six weeks each subject displayed distaste for the diet and definite changes of pellagra, characterized by dermatitis (figs. 2 and 3) and mild redness of the tongue and mouth; two of the patients began to vomit. When the diet was changed to an adequate one, they quickly improved.

COMMENT

It must be admitted that clinicians cannot always distinguish between sunburn in normal persons and the erythematous lesions of pellagra, with the result that the diagnosis of pellagra is often made only by means of the history with little or no consideration for the fact that in a person receiving either an inadequate diet or a normal one sunburn might develop in a similar manner. At present there is a tendency to diagnose as pellagrous all symmetrically distributed cutaneous lesions on the hands of persons existing on a poor diet. Prolonged exposure to sunlight is toxic in varying degrees to normal persons, and it is recognized that sunlight in general augments the severity of certain diseases of the skin. In the clinic with which I am associated, where alcoholism predisposes to dietary insufficiency, pellagra occurs throughout the winter months. In the South, where there is a definite increase in the frequency of pellagra in the spring, the incidence of the disease is decidedly less during July and August, when there is certainly no decrease in sunshine. Moreover, pellagra develops in Negroes, who are naturally somewhat protected from sunlight by the pigment of the skin.

Many writers maintain that the dermatitis of pellagra occurs only on the exposed surfaces, but that is not true of patients in this clinic, for the feet, perineal region, elbows and other parts of the body are frequently involved. This study has demonstrated that pellagrous lesions of the skin may develop in the absence of sunlight and that exposure of areas of pellagrous dermatitis either to large doses of ultraviolet radiation or to direct sunlight does not prevent healing of the lesions, even when the patient is limited to a pellagra-producing diet. (All these patients took the full diet of 2,900 calories, low in pellagra-preventive substances, each day.) These observations, however, do not prove that sunlight may not exert an irritating effect, and they certainly do not eliminate the possibility that exposure to sunlight may precipitate the early lesions of the skin. According to the studies carried on in this clinic, the dermatitis of pellagra never remains static; it either improves or becomes worse, thus making controlled experimentation of a quantitative nature for a period of time almost impossible.

Recently, Ruffin and Smith studied pellagrous dermatitis and reported that the exposure to sunlight of some pellagrins on a pellagra-producing diet causes the appearance of the dermal changes of the disease in the exposed area. Even if one accepts it as fact that the induced cutaneous changes in their cases were pellagrous and not due to sunburn, it is impossible to state that the relationship between exposure to sunlight and the development of pellagrous dermatitis is definitely one of cause and effect. The histories in two of their cases clearly showed

that oral lesions of pellagra and diarrhea developed simultaneously with the appearance of dermatitis at the area of exposure. Should not one conclude, then, that if sunlight produced the dermatitis it caused the stomatitis, glossitis and diarrhea too? It is possible that the patients may have had a general relapse, which often occurs in this disease.

Since so many observers during the past two hundred years have believed that the lesions of pellagra are caused by sunlight, serious consideration should be given to the possibility of a relationship between them. On purely theoretical grounds it seems probable either that the sun acts as an irritant, its heat hastening the cutaneous eruption, or that it effects a specific chemical change which in turn produces dermatitis. Since my studies have shown that the dermal changes of pellagra can be induced in the absence of sunlight and since the pellagrous changes of the skin are often observed over the points liable to irritation, such as the hands, elbows, axillae, skin under the breasts, feet, sacrum and perineum, it seems reasonable to suggest that sufficient irritation of any kind might predispose the area to localization of the dermatitis. The sun in North Carolina, where the studies of Ruffin and Smith were carried out, gives more direct rays which are less filtered by smoke than in Cleveland, where my studies were made. For this reason, it is impossible to state that the characteristic dermatitis of pellagra cannot be produced at times by sunlight in the manner described by these investigators. From a practical standpoint, however, it should be borne in mind that the disappearance of dermatitis does not necessarily mean the cure of pellagra. The other manifestations of the disease often exist without involvement of the skin and may even cause the death of the patient without reappearance of the dermatitis.

Although pellagra received its name because of its rather characteristic cutaneous lesions, it should not be considered purely a disease of the skin any more than syphilis or smallpox, both of which have changes in the skin of diagnostic value. Since cutaneous manifestations are common to many systemic conditions, the finding of them in pellagra by analogy should not be surprising and should lead to their interpretation as a local reaction to a systemic disease of diagnostic importance. There is no entirely satisfactory explanation at this time as to why the skin should or should not be involved in pellagra, but if the fact is accepted that measles is likely to begin on the face, scarlet fever on the body and typhoid fever with rose spots on the abdomen, it does not seem too novel to suggest that pellagra has a predilection for the hands, face, feet, knees, perineum and other sites. The affinity of various diseases for certain organs and locations is still inexplicable.

SUMMARY AND CONCLUSIONS

It has been shown in the present study that pellagrous lesions occur in the absence of sunlight and that they may heal in the presence of exposure to direct sunlight or to ultraviolet radiation.

It is suggested that pellagra should be considered not as a disease of the skin but as a systemic condition which in itself is the real cause of pellagrous dermatitis rather than any incidental or experimental exposure to the rays of the sun.

It is pointed out that under certain conditions sunlight may act as an irritant and precipitate the cutaneous lesions; but this at present is still a matter of conjecture.

INTERPRETATION OF ABNORMAL DEXTROSE TOLERANCE CURVES OCCURRING IN TOXEMIA IN TERMS OF LIVER FUNCTION

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AND

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CHICAGO

The decreased tolerance for carbohydrate which occurs in patients with acute infectious diseases has been confirmed recently by Williams and Dick,[1] whose paper contains an excellent review of the previous literature. A similar disturbance in carbohydrate metabolism has been demonstrated in experimentally induced toxemias in animals.[2] The "diabetic" type of dextrose tolerance curve obtained in the conditions mentioned has been interpreted by some as being due to a lack of endogenous insulin, consequent to the functional impairment of the islands of Langerhans.[3] Others have ascribed the phenomenon to an interference with the action of the available insulin, whether of endogenous or of exogenous origin.[4]

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From the Metabolic Laboratory of the Department of Physiology, Michael Reese Hospital, and the Department of Physiology, University of Chicago.

1. Williams, J. L., and Dick, G. F.: Decreased Dextrose Tolerance in Acute Infectious Diseases, Arch. Int. Med. **50**:801 (Dec.) 1932.

2. (*a*) Tisdall, F. F.; Drake, T. G. H., and Brown, A.: The Production of a Lowered Carbohydrate Tolerance in Dogs, Am. J. Dis. Child. **32**:854 (Dec.) 1926. (*b*) Sweeney, J. S., and Lackey, R. W.: The Effect of Toxemia on Tolerance for Dextrose, Arch. Int. Med. **41**:257 (Feb.) 1928. (*c*) Sweeney, J. S.: Effect of Toxemia on the Tolerance for Dextrose and on the Action of Insulin, ibid. **41**: 420 (March) 1928. (*d*) Schwentker, F. F., and Noel, W. W.: The Circulatory Failure of Diphtheria: The Carbohydrate Metabolism in Diphtheria Intoxication, Bull. Johns Hopkins Hosp. **46**:259, 1930. (*e*) Lawrence, R. D., and Buckley, M. B.: The Inhibition of Insulin Action by Toxaemias and Its Explanation: I. The Effect of Diphtheria Toxin on Blood Sugar and Insulin Action in Rabbits, Brit. J. Exper. Path. **8**:58, 1927. (*f*) Sweeney, J. S.; Barshop, N., and LoBello, L. C.: Effect of Toxemia on the Tolerance for Dextrose and on the Action of Insulin, Arch. Int. Med. **53**:689 (May) 1934. (*g*) Sweeney, J. S.; Barshop, N.; LoBello, L. C., and Rosenthal, R. S.: Effect of Toxemia on the Tolerance for Dextrose and on the Action of Insulin: II. ibid. **54**:381 (Sept.) 1934.

3. Williams and Dick.[1] Sweeney and Lackey.[2b] Sweeney.[2c]

4. Lawrence and Buckley.[2e] Sweeney, Barshop and LoBello.[2f] Sweeney, Barshop, LoBello and Rosenthal.[2g]

The former interpretation is based on the belief that the normal dextrose tolerance curve is dependent on an increase in the circulating insulin consequent to pancreatic stimulation by the administered dextrose. We have shown recently, however, that a normal dextrose tolerance curve may be obtained in a completely depancreatized dog which is receiving a constant injection of insulin and dextrose just sufficient to maintain the blood sugar at a constant level.[5] An animal in this condition, moreover, shows a hypoglycemic reaction at least as great as that of a normal dog following the cessation of prolonged administration of dextrose.[6] The absence of the pancreas precludes the possibility of an extra secretion of insulin into the blood stream following the administration of sugar. Since the normal reactions to the administration of dextrose do not require the secretion of additional insulin, it seems clear that the abnormal curves of toxemia do not result from the lack of extra secretion.

Our previous work [5] has shown that a hepatectomized dog receiving a constant injection of dextrose just sufficient to maintain the blood sugar at a constant level yields consistently "diabetic" dextrose tolerance curves. Hence, the presence of the normal liver is essential to the normal response. From the results of simultaneous observations on the blood sugar content of the blood entering and leaving the liver during tests [5] for dextrose tolerance, it was concluded that in the presence of a sufficiency of circulating insulin, but not necessarily of an extra secretion from the pancreas, the normal liver responds to administered dextrose by decreasing its output of blood sugar, which it previously has been supplying from its own resources. The existence of such a homeostatic mechanism of the liver as we have postulated has been confirmed substantially in a recent paper by Tsai and Yi,[7] who calculated the quantity of sugar entering and leaving the liver by means of a flowmeter. This mechanism of the liver may be visualized more easily perhaps as being analogous to the control of temperature by a thermostatically regulated furnace. In this analogy the endocrine balance, as represented by the integrated influences of insulin and the hormones of the anterior lobe of the pituitary, the thyroid and the adrenal glands, corresponds to the factors determining the sensitivity and the threshold of the thermostat. The blood sugar level corresponds to the room temperature and is the stimulus which activates the regulatory mechanism of the liver.

5. Soskin, S.; Allweiss, M. D., and Cohen, D. J.: Influence of the Pancreas and the Liver upon the Dextrose Tolerance Curve, Am. J. Physiol. **109**:155, 1934.

6. Soskin, S., and Allweiss, M. D.: The Hypoglycemic Phase of the Dextrose Tolerance Curve, Am. J. Physiol. **110**:4, 1934.

7. Tsai, C., and Yi, C. L.: Carbohydrate Metabolism of the Liver: III. The Sugar Intake During Glucose Absorption, Chinese J. Physiol. **8**:273, 1934.

From the foregoing experiments it appeared probable that toxemia interferes with the homeostatic mechanism of the liver already described through its effects on the liver itself. It therefore seemed of interest to attempt to demonstrate by our methods the influence of experimentally induced toxemia on the dextrose tolerance curve in the absence of the pancreas.

METHODS

All these experiments were performed on unanesthetized normal and depancreatized dogs, which were trained to lie quietly on an animal board while the injections were given and the samples of blood taken by means of venous puncture with hypodermic needles. As in our previous work, the test sugar always was given intravenously to avoid variations due to absorption. Food and insulin were withheld for eighteen hours prior to each test. The dose of diphtheria toxin [8] required to produce rapid onset of toxic symptoms and disturbances in carbohydrate metabolism in our animals was found, by preliminary studies, to range from 80 to 160 minimal lethal doses per kilogram of body weight, administered intravenously. Less toxin was necessary in the depancreatized dogs than in the normal dogs.

In all experiments a preliminary test for dextrose tolerance was made, at the termination of which the suitable dose of toxin was administered. One hour later a second test for dextrose tolerance was made. Control experiments in which the administered toxin was rendered inert by boiling for five minutes were also done. The procedure with the depancreatized dogs was identical with that employed on the normal dogs except that a constant blood sugar level was first established by the constant injection of dextrose plus insulin, as described in our previous articles.[9] Once they were adjusted, the injections were continued unchanged throughout the experiment.

RESULTS

The effect of the intravenous administration of diphtheria toxin on the subsequent dextrose tolerance curve was uniformly distinct in all our experiments. Typical results are detailed in table 1 and illustrated by charts 1 and 2.

It may be seen that in normal dogs the administration of the toxin caused a definitely abnormal prolongation of the subsequent tolerance curve (table 1, fig. 1, solid lines), while the injection of boiled toxin was without effect (table 1, fig. 1, broken lines). In the depancreatized dogs (table 1, fig. 2) the administration of toxin was followed by curves even more "diabetic" than those obtained after the injection of toxin into the normal animals, although the preliminary tolerance curves were quite normal.

SUMMARY AND COMMENT

Our results show:

1. The acute toxemia resulting from the intravenous administration of adequate amounts of diphtheria toxin always brings about an

8. Eli Lilly & Co. supplied the standardized potent diphtheria toxin.

9. Soskin, Allweiss and Cohen.[5] Soskin and Allweiss.[6]

Effect of Intravenous Administration of Diphtheria Toxin on the Subsequent Dextrose Tolerance in Normal and Depancreatized Dogs

Subject	No.	First Dextrose Tolerance Test*							Diphtheria Toxin Injected Intravenously	Second Dextrose Tolerance Test*						
		Before	30 Min.	60 Min.	90 Min.	120 Min.	150 Min.	180 Min.		Before	30 Min.	60 Min.	90 Min.	120 Min.	150 Min.	180 Min.
Normal dog	1	93	312	206	85	76	...	71	160 M.L.D. per kilogram	74	322	243	171	138	102	...
	2	60	283	84	48	53	63	..	160 M.L.D. per kilogram (boiled for five minutes)	55	226	60	20	19	21	23
Depancreatized dog (blood sugar maintained at a constant level)	1	123	354	197	146	131	124	100	80 M.L.D. per kilogram	65	410	286	208	...	181	211
	2	50	193	121	96	81	62	70	80 M.L.D. per kilogram	106	297	216	222	238	...	...
	3	123	317	203	159	131	108	97	80 M.L.D. per kilogram	93	...	254	234	227	216	208

* The values are expressed in milligrams per hundred cubic centimeters of blood.

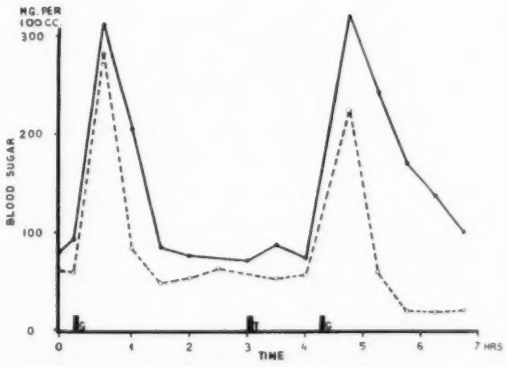

Fig. 1.—Results of tests for dextrose tolerance in normal dogs before and after the administration of toxin. In the experiment represented by the broken lines the toxin was boiled for five minutes before administration. *G* indicates the administration of the test sugar and *T* the administration of the toxin.

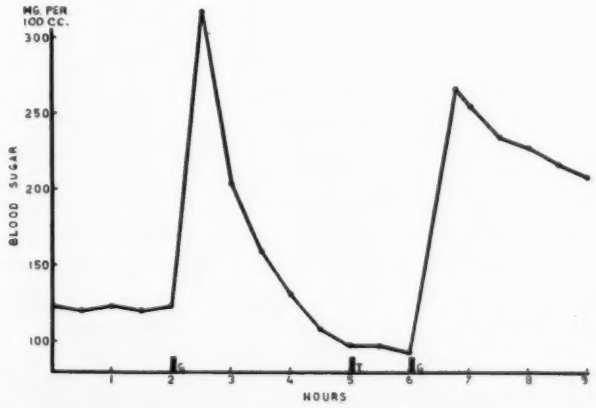

Fig. 2.—Results of tests for dextrose tolerance in a depancreatized dog receiving throughout the experiment a constant injection of dextrose plus insulin just sufficient to maintain the blood sugar at a constant level. *G* indicates the administration of the test sugar and *T* the administration of the toxin.

abnormal prolongation of the subsequent dextrose tolerance curve. This effect is probably due to the toxin per se, since it is not obtained with boiled toxin.

2. The normal dextrose tolerance curve obtained in a completely depancreatized dog receiving a constant injection of insulin plus dextrose just sufficient to maintain the blood sugar at a constant level becomes definitely "diabetic" after the administration of toxin.

It is apparent that toxemia does not produce its effects on the dextrose tolerance curve by acting through the pancreas. Furthermore, Yannet and Darrow [10] found no evidence of any gross disturbance in the oxidation of carbohydrates during the course of diphtheritic intoxication produced by the intravenous injection of diphtheria toxin into rabbits. They did observe definite changes in the liver, and they concluded that the observed disturbances in carbohydrate metabolism were due to a failure in hepatic function. Our results support this conclusion and indicate that the hepatic function which is interfered with is that by which the liver normally strives to maintain a constant blood sugar level, by decreasing its own output of sugar in response to the influx of exogenous sugar.

Our work is also in accord with that of Althausen and Thoenes,[11] who concluded that the first effect of phosphorus, when given in toxic amounts, was to act as an irritant to the glycogenolytic mechanism of the liver. That this may apply to other functions of the liver is suggested by the findings of Whipple, Peightal and Clark,[12] who reported hypersecretion of phenoltetrachlorphthalein by the liver after small doses of phosphorus were given, which they attributed to the irritative effect of this toxin on the secreting parenchyma. It seems reasonable that this hyperirritability of the liver cells should limit the extent of the hepatic inhibition which normally follows a given rise in blood sugar. However, the limitation of the capacity of the liver to respond in this manner may become evident after the administration of the relatively large test dose of dextrose while the organism, possibly with the aid of other mechanisms of the body, is still able to make a sufficient

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11. Althausen, T. L., and Thoenes, E.: Influences on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes: II. Phosphorus Poisoning, Arch. Int. Med. **50**:58 (July) 1932.

12. Whipple, G. H.; Peightal, T. C., and Clark, A. H.: Tests for Hepatic Function and Disease Under Experimental Conditions: Phenoltetrachlorphthalein, Bull. Johns Hopkins Hosp. **24**:343, 1913.

adjustment for smaller variations in blood sugar. Hence, a normal blood sugar level may often be maintained in a toxic animal which, nevertheless, yields a "diabetic" tolerance curve.

In their more recent reports, Sweeney and his associates [2g] concluded that toxemia acts not by merely suppressing the endogenous insulin supply but rather by interfering with the function of insulin, whether it is endogenous or exogenous in origin. This is in entire agreement with our own conclusions in the sense that toxemia interferes with the normal "sensitization" by insulin of the compensatory response of the liver to an increase in blood sugar. To revert to our previous analogy, toxemia represents an interference with the sensitivity of the thermostat. This view of so-called "insulin resistance" removes the therapeutic incongruity of treating already impaired carbohydrate metabolism by the administration of still more carbohydrate. From our standpoint, the treatment with carbohydrate in toxemic states increases the stimulus to the insensitive mechanism. It may be compared to the stimulation of the secretion of urine in the damaged kidney by the administration of urea.

In the light of a previous article which furnishes strong proof for the "overproduction theory" of diabetes mellitus,[13] this disease may be considered as a condition in which the threshold for the stimulation of the homeostatic mechanism of the liver is abnormally high. The liver, because of an endocrine imbalance,[5] continues to pour out blood sugar in the presence of even marked hyperglycemia. Since it is the threshold, and not the sensitivity, of the homeostatic mechanism which is affected, the administration of insulin lowers the threshold so that regulation at the normal blood sugar level becomes possible. The success of the more recent diets high in carbohydrates, as advocated by Porges and Adlersberg,[14] Sansum [15] and others, is not surprising when considered in terms of the magnitude of the stimulus to the regulatory mechanism of the liver. However, when infection intervenes, the sensitivity as well as the threshold is affected, and the diabetic organism becomes "insulin resistant." As might be predicted from these results, it has been our experience [16] that the addition of a high intake of carbohydrate may be of great assistance in the treatment of patients with diabetes who are resistant to insulin when the use of large amounts of insulin alone has failed to control the metabolic disturbance.

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13. Soskin, S.: The Utilization of Carbohydrate by Totally Depancreatized Dogs Receiving No Insulin, J. Nutrition **3**:99, 1930.

14. Porges, O., and Adlersberg, D.: Die Behandlung der Zuckerkrankheit mit fettarmer Kost, Berlin, Urban and Schwarzenberg, 1929.

15. Sansum, W. D.; Gray, P. A., and Bowden, R.: The Treatment of Diabetes Mellitus with Higher Carbohydrate Diets, New York, Harper & Brothers, 1929.

16. Strouse, S., and Soskin, S.: Unpublished data.

CONCLUSIONS

1. The abnormal dextrose tolerance curves occurring in cases of toxemia are due to the effects of the toxin on the liver and not on the pancreas.

2. The toxin interferes with the homeostatic mechanism of the liver which we have described, i. e., the mechanism by which the liver decreases its supply of blood sugar in response to an influx of exogenous sugar.

3. The interpretation of abnormal dextrose tolerance curves in terms of the function of the liver, whether such tests occur in toxemia, diabetes or other conditions, relates all such curves to a common underlying mechanism instead of to various factors as formerly. This not only renders the curves themselves more intelligible but gives a more rational view of "insulin resistance," the use of carbohydrate therapy and other related phenomena.

The Department of Chemistry assisted in the chemical analyses, and Miss Bernice Huddlestun gave technical assistance in this study.

DIFFERENTIAL DIAGNOSIS OF RUBELLA

USE OF THE SCHILLING DIFFERENTIAL LEUKOCYTE COUNT

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ST. LOUIS

The differential diagnosis of rubella is of importance for two reasons: first, to distinguish it from toxic rashes and thus prevent the spread of the disease and, second, to distinguish it from scarlet fever and measles and thus permit the care necessary in these more serious conditions. Rubella is usually considered a benign disease. Deaths, however, occur. Carrieu, Lamy and Bouchet [1] reported two fatal cases in young children. Belson [2] stated that from 1914 through 1929 there were 26 deaths in 35,879 cases reported in Massachusetts.

Complications are rare, but may be serious. Geiger [3] described an epidemic in which arthritis was frequent; otitis media, acute nephritis and endocarditis also were observed. Severe symptomatic purpura haemorrhagica with recovery has been described by Pitten [4] and Gunn.[5] Suppuration of the cervical lymph nodes, bronchitis and epistaxis occurred in the epidemic reported by Carrieu, Lamy and Bouchet. Involvement of joints, disturbance of the central nervous system and bronchopneumonia occurred in three severe cases reported by Potter.[6] Lindberg [7] observed polyarthritis and acute stomatitis as complications. It seems important, considering these possible serious though rare complications, to make every effort to prevent the spread of the disease by making an accurate diagnosis.

From the Department of Medicine, Washington University School of Medicine, and the City Isolation Hospital.

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2. Belson, M. O.: Clinical Features of an Epidemic of Rubella, New England J. Med. **203**:1076 (Nov. 27) 1930.

3. Geiger, J. C.: Epidemic of German Measles in City Adjacent to an Army Cantonment, J. A. M. A. **70**:1818 (June 15) 1918.

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The exanthem of rubella may at times be characteristic, but in many cases it is difficult to distinguish it from that seen in measles, scarlatina or toxic rashes. The chief criteria usually employed in differential diagnosis are:

Rubella.—The incubation period is seventeen or eighteen days. Enlargement of lymph nodes in the cervical, mastoid and occipital regions begins several days before the appearance of the rash. The rash is discrete and papular, with smaller papules than in measles, and is pink rather than red. It fades in from one to three days. There are few constitutional symptoms and little fever.

Measles.—The incubation period is fourteen days. The onset is preceded by catarrhal symptoms. Koplik's spots are present. The rash consists of dark red macules which become maculopapular and occur in crescentic blotches. Constitutional symptoms may be marked. The temperature is from 102 to 104 F. The rash remains longer than in rubella. Sometimes there is desquamation, and usually there is pigmentation.

Scarlatina.—There is a seven day incubation period. The onset is abrupt, with sore throat, high fever and vomiting. There are a circumoral pallor and a fine red macular rash which becomes confluent and is more marked in the folds. There are severe constitutional symptoms. Desquamation occurs.

Toxic Rashes.—These have an irregular distribution and are polymorphic. Usually there is no glandular enlargement or fever.

We have found that the differential leukocyte count, with the use of Schilling's classification, is an additional and important diagnostic aid. We believe that failure to recognize a characteristic differential blood picture in rubella has resulted from: (1) misleading observations of early authors, (2) the lack of a practical and satisfactory classification of the leukocytes for clinical purposes, now available in the Schilling count and (3) the lack of careful serial counts throughout the disease in a large number of cases.

Many textbooks [8] state that the changes in the blood are similar to those in measles and consist of a tendency to leukopenia, an increase in monocytes and lymphocytes and the occurrence of plasma and Türk cells. Dowd [9] states that there is no characteristic change in the blood

8. Pepper, O. H. P., and Farley, D. L.: Practical Hematological Diagnosis, Philadelphia, W. B. Saunders Company, 1933, p. 440. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods, Philadelphia, W. B. Saunders Company, 1932, p. 259. Piney, A.: Diseases of the Blood, Philadelphia, P. Blakiston's Son & Co., 1928, p. 153. Osgood, E. E., and Haskins, H. D.: Textbook of Laboratory Diagnosis, Philadelphia, P. Blakiston's Son & Co., 1931, p. 184.

9. Dowd, H. L.: Rubella, in Cecil, R. L.: Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1933, p. 301.

in rubella. Schilling [10] asserted that the "gay" blood picture occurs, but gave no sample counts.

Naegeli [11] stated that plasma cells are present in very large numbers, sometimes reaching 30 per cent. This observation focused the attention of succeeding hematologists on the bizarre plasma and Türk cells rather than on changes perhaps more characteristic. Hickling,[12] in fourteen differential counts taken at various stages of the illness in eleven cases, observed no characteristic change except increased plasma cells (averaging 4.5 per cent). His total leukocyte counts varied from 6,900 to 13,700. Eosinophils averaged 2.4 per cent. Lindberg [7] observed leukopenia early in the disease (from 4,000 to 8,000 leukocytes). Plasma cells occurred in 76 per cent of his cases but averaged only 1.5 per cent. Eosinophils averaged from 1 to 1.5 per cent. He gives this as a typical count: white cells, 5,300 per cubic millimeter; polymorphonuclears, 65 per cent; lymphocytes, 30 per cent; basophils, 2 per cent; eosinophils, 1 per cent, and plasma cells, 2 per cent.

Carroll [13] observed leukopenia on the first day, an increase in the eosinophils on the third to the fifth day and a rise in the lymphocytes from the fourth to the fifth day onward. He stated that the polymorphonuclear neutrophils are not much affected except for a moderate reduction in number from the fourth or fifth day to the sixth or seventh day. He observed that plasma cells were increased, reaching a maximum of from 3 to 11 per cent on the third day. Türk cells were increased, but were less numerous and less constantly present.

Considerable confusion will be seen to result if an attempt is made to correlate and interpret the observations of the various authors cited.

During the spring months of 1932 and 1933 serial counts by the Schilling method were done in thirty cases of rubella throughout the course of the disease. A clear picture soon began to present itself as characteristic. This was very different in the early stages from that obtained in scarlatina, measles or toxic rashes.

The supposedly characteristic plasma and Türk cells were entirely absent from many slides. Lindberg [7] observed that they were absent in one fourth of his cases. These cells are difficult to identify, and hematologists differ greatly in describing them. The plasma cell has abundant basophil cytoplasm, usually vacuolated, and an eccentric

10. Schilling, V.: The Blood Picture and Its Clinical Significance, translated by R. B. H. Gradwohl, St. Louis, C. V. Mosby Company, 1929, pp. 268 and 297.

11. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Berlin, Julius Springer, 1923.

12. Hickling, R. A.: The Significance of Hemic Plasma Cells in Various Infective Conditions, J. Hyg. **24**:120 (Oct.) 1925.

13. Carroll, John V. : The Blood Count in Rubella, Lancet **1**:182 (Jan. 27) 1934.

nucleus bordered by a clear space in the cytoplasm (*Zellhof*). The Türk irritation cell morphologically comes between the plasma cell and the lymphocyte. It is often difficult to distinguish a plasma cell, a Türk cell and a lymphocyte with deep basophil cytoplasm. The Türk cell has no vacuoles or *Zellhöfe* and is the same size or slightly larger than the average lymphocyte. The nucleus is usually eccentric. The Türk cell stains more evenly, while the plasma cell is characteristically foamy. Piney [14] stated that the Türk cell is a modified lymphocyte, but that it is uncertain whether it is a stage in the development of the plasma cell.

Since there is considerable disagreement as to the appearance of these cells, and since even experienced hematologists have difficulty at times in distinguishing them from lymphocytes, to which they are closely related, we have included both plasma and Türk cells with our lymphocytes in the tables. A system of hematologic diagnosis must be simple to be useful. The differential diagnosis of the exanthems is the general practitioner's problem. He cannot be expected to identify unusual forms of cells, but the simple principles of the Schilling classification are easily learned and used.

We observed plasma cells occurring inconstantly, reaching 6 per cent in one case on the third day, but averaging about 2 per cent in the early days. Türk cells averaged about 1 per cent. We agree with Hickling [12] and Carroll [13] that these cells appear also in measles, but in smaller numbers and less constantly. For those prepared to identify them they are an additional aid in diagnosis.

We found no significant differences between the counts in children and adults. Our youngest patients were two, aged 7. No complications were observed in our series of thirty cases.

Table 1 gives the serial counts on successive days of the disease, the date of onset being considered the day of appearance of the rash. At the onset the neutrophils constitute only about 60 per cent of the white cells, but there is a marked rise in the stab cells. The appearance of juvenile forms (metamyelocytes) is rare. The lymphocytes and monocytes are relatively numerous, while eosinophils tend to be retained in normal numbers, not disappearing as in most acute infections. The total white cell count averages less than 5,000 per cubic millimeter, but some counts fall within the normal range. As the mild elevation in temperature subsides and the rash disappears the total neutrophil count falls, reaching a low point of about 48 per cent on the fourth day. The percentage of stab cells rapidly falls, reaching normal between the eighth and twelfth days. Meanwhile the lymphocytes and monocytes rise, reaching a maximum about the fourth day. The eosinophils rise, reaching a maximum averaging 2 per cent but sometimes reaching 10 per cent, between the third and sixth days. The total leukocytes rise

14. Piney, A.: Plasma Cell Leukemia, Folia haemat. **30**:173 (Aug.) 1924.

TABLE 1.—*Serial Differential Blood Counts in Rubella*

Day	Number of Patients	Baso-phils	Eosinophils		Myelo-cytes	Juvenile Forms	Stab Cells		Segmented Forms		Lymphocytes		Monocytes		White Cells		
			Average	Range			Average	Range	Average	Range	Average	Range	Average	Range	Average	Range	Number
1	11	0	0.9	0-4	0	0	15.4	9-19	44.7	30-54	34.6	25-48	4.8	1-12	4,982	3,450-7,800	11
2	23	0	1.1	0-4	0	0	14.4	8-24	41.7	26-54	38.0	23-50	4.9	2-8	5,441	3,300-9,000	18
3	25	0	1.9	0-5	0	0	11.8	5-18	40.6	25-62	39.9	21-58	5.7	3-9	5,844	4,150-8,900	9
4	22	0	1.9	0-5	0	0	8.4	5-16	39.6	18-60	43.7	28-62	6.0	2-10	7,690	6,400-9,000	4
5	18	0	2.1	0-10	0	0	6.9	2-13	43.8	32-63	42.8	28-59	5.3	2-9	7,950	.....	1
6	21	0	2.0	0-4	0	0	5.5	3-11	46.1	30-61	41.2	26-58	4.7	1-10	7,833	6,250-9,250	3
7	16	0	1.9	0-4	0	0	5.3	3-9	48.6	32-65	39.6	23-56	4.6	2-8	8,350	8,100-8,600	2
8	9	0	1.3	0-3	0	0	4.8	2-8	51.3	36-64	38.1	24-52	4.3	2-6	9,150	.....	1

gradually from the first day onward, reaching normal about the seventh or eighth day. By the eighth day a definite approach toward normal is apparent in all respects, and within the next few days normal figures are reached.

TABLE 2.—*Typical Counts in Rubella* *

Day	Baso-phils	Eosino-phils	Myelo-cytes	Juvenile Forms	Stab Cells	Segmented Forms	Lympho-cytes	Mono-cytes
1	0	0	0	0	18	46	32	4
2	0	0	0	0	11	41	41	7
3	0	1	0	0	10	37	49	4
4	0	3	0	0	8	42	32	9
5	0	0	0	0	8	46	41	5
6	0	1	0	0	4	60	34	1
7	0	1	0	0	6	54	31	8

* The patient was a white man, aged 30. The total leukocyte count on the first day was 3,650. The rash and fever were gone by the third day.

TABLE 3.—*Typical Counts in Measles* *

Day	White Cells	Baso-phils	Eosino-phils	Myelo-cytes	Juvenile Forms	Stab Cells	Segmented Forms	Lympho-cytes	Mono-cytes
1	6,200	0	1	0	4	12	55	25	3
2	6,000	0	2	0	6	16	55	21	0
3	6,300	0	2	0	3	14	60	19	2
4	6,100	0	0	0	0	10	63	23	4
6	6,800	0	2	0	0	9	57	27	5
8	7,200	0	1	0	0	10	55	30	4
10	8,400	0	0	0	0	8	53	36	3
12	8,100	0	2	0	0	8	46	41	3
14	8,250	0	1	0	0	4	58	33	4

* The patient was a white boy, aged 12. The temperature was 102 F. on the first day, 103 F. on the second day, and 101 F. on the third day. On the fourth day the fever was gone. On the sixth day the rash was gone.

TABLE 4.—*Typical Counts in Scarlatina* *

Day	White Cells	Baso-phils	Eosino-phils	Myelo-cytes	Juvenile Forms	Stab Cells	Segmented Forms	Lympho-cytes	Mono-cytes
1	18,200	0	2	0	8	20	56	14	0
2	14,400	0	2	0	6	18	56	18	0
3	12,100	0	4	0	3	15	55	20	3
4	11,000	0	5	0	0	10	58	21	6
5	10,000	0	3	0	0	9	62	20	6
6	11,200	0	1	0	0	9	62	19	9
7	8,000	0	0	0	0	8	62	25	5
10	8,300	0	1	0	0	6	53	36	4
12	7,600	0	1	0	0	4	61	30	4
14	8,800	0	1	0	0	3	62	30	4

* The patient was a white boy, aged 7.

Table 2 gives the counts in a typical case of rubella occurring in a white man, 30 years old.

When the counts in rubella are compared with those obtained in typical cases of scarlatina, measles and toxic rashes, definite differences are at once apparent (tables 3, 4 and 5).

In measles (the counts by Hickling,[12] Bunting and Thewlis[15] and Schilling[10] are similar to ours) there is less tendency to leukopenia; there is a more marked "defense reaction" with a higher number of neutrophils, among which stab cells are more numerous and juvenile forms appear. Lymphocytes are correspondingly less numerous. Monocytes and eosinophils tend to follow curves similar to those in rubella. The higher neutrophil count, with the appearance of juvenile forms,

TABLE 5.—*Typical Counts in Toxic Rash (Drug?)* *

Day	White Cells	Baso-phils	Eosino-phils	Myelo-cytes	Juvenile Forms	Stab Cells	Segmented Forms	Lympho-cytes	Mono-cytes
1	10,000	0	3	0	0	6	68	20	3
2	9,400	0	6	0	0	5	69	18	2
3	8,300	0	2	0	0	4	60	31	3
4	8,350	0	3	0	0	2	56	37	2
5	8,200	0	2	0	0	3	57	35	2

* The patient was a white boy, aged 8. The rash resembled that of both scarlet fever and measles. It lasted for four days. There was no fever.

TABLE 6.—*Rubella Followed by Scarlatina* *

Day	White Cells	Eosino-phils	Stab Cells	Segmented Forms	Lympho-cytes	Mono-cytes	Comment
3	6,700	0	18	33	41	8	Note fall in stab cells and rise in lymphocytes during recovery from rubella
4	.....	1	11	45	40	3	
5	.....	1	11	50	34	4	
6	.....	1	11	52	32	4	Lymphocytes fall suddenly;
7	(first day of scarlatina; sore throat)	1	9	57	29	4	segmented forms increase, and fall in stab cells is arrested
8	(second day of scarlatina; rash appeared)						
9	19,450						
10	12,550						
11	.....	1	9	69	16	5	
12	.....	1	8	63	24	4	

* The patient was a white girl, aged 19. Both the rubella and the scarlatina were typical and uncomplicated.

and the relatively low percentage of lymphocytes should be helpful in distinguishing doubtful cases from rubella.

In scarlet fever there is a very high leukocyte count with a very high count for total neutrophils, stab cells typically reaching 20 per cent or more and juvenile forms 8 per cent or more. Lymphocytes are low, being 14 per cent or less. Eosinophils tend to be retained and to rise during recovery. The blood differential count in scarlet fever should never be confused with that in rubella.

15. Bunting, C. H., and Thewlis, E.: Leukocytic Reactions in Smallpox, Chickenpox, Measles and Mumps, Arch. Path. **1**:189 (Feb.) 1926.

In drug or toxic rashes the total leukocyte count may be slightly increased, with a slight rise in neutrophils and stab cells. Eosinophils are usually increased.

Of the greatest importance in the study of differential leukocyte counts in acute infections is the recognition that the hemogram may change considerably from day to day, and that counts must be inter-

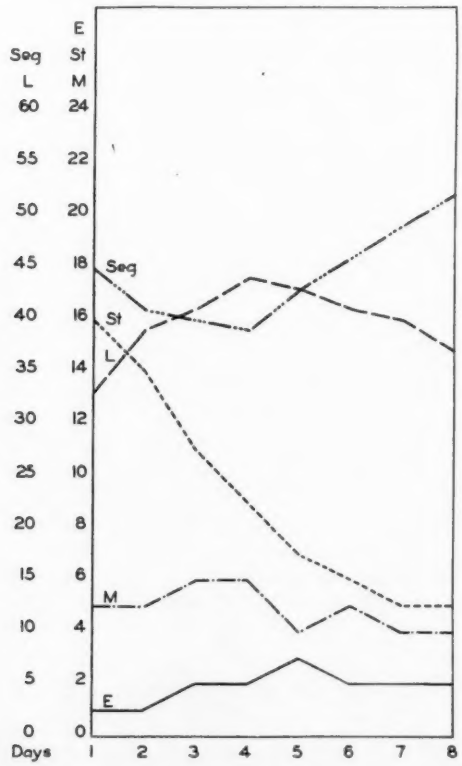

Chart 1.—Curve showing changes in the leukocyte count in rubella. In this chart and in chart 2 the letters have the following meanings: *E* indicates eosinophils; *St*, stab forms; *Seg*, segmental forms; *L*, lymphocytes; *M*, mononuclears, and *J*, juvenile forms.

preted according to the stage and duration of the illness. Curves charting the changes in rubella and measles serve to emphasize that the rapidity of rise and fall of the various component classes of leukocytes,

as well as the actual percentage of height, is helpful in making the diagnosis.

In one of our patients scarlatina developed immediately following the attack of rubella. The rapid rise in the neutrophils and fall in the lymphocytes, while the stab cells were arrested in their rapid fall, are well seen in table 6.

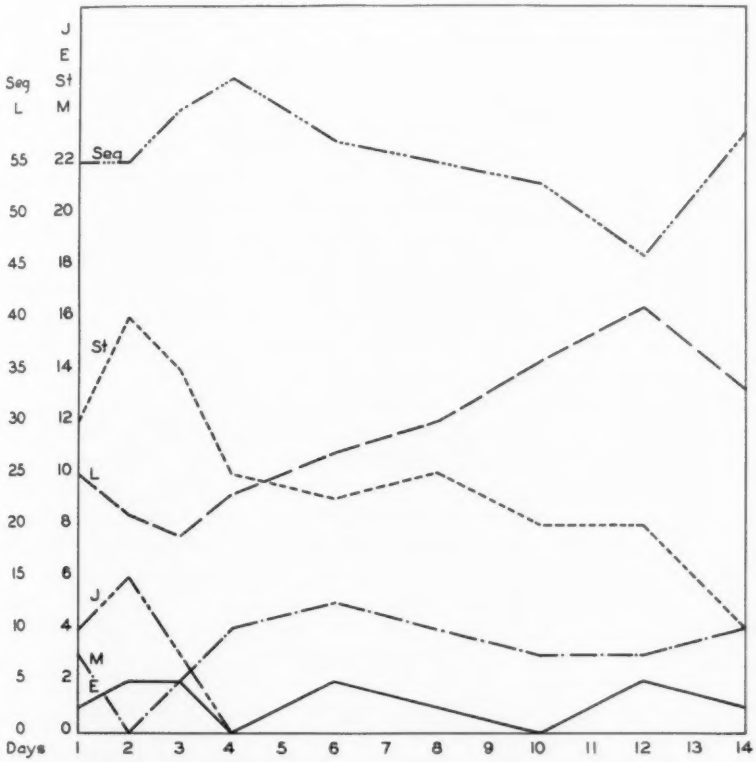

Chart 2.—Curves showing changes in the leukocyte count in measles.

CONCLUSIONS

1. In a study of thirty cases of rubella the use of the Schilling differential leukocyte count was found to be an important aid in making the diagnosis.

2. Serial differential counts in measles, scarlatina and toxic rashes—conditions which may be confused with rubella—differ significantly from counts obtained in rubella.

RENAL AMYLOIDOSIS

CLINICAL COURSE AND PATHOLOGIC LESIONS IN SIXTEEN CASES

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While renal amyloidosis is a common complication of tuberculosis, apparently it has not received much attention from English-speaking physicians, so far as published reports are concerned. Reports of only 14 cases of amyloid in the kidneys were found in a review of the literature from Jan. 1, 1917, to Dec. 31, 1932. We found the following cases reported, including those of both tuberculous and nontuberculous origin:

Noble and Major [1] reported 3 cases, 2 of which occurred in conjunction with chronic osteomyelitis (presumably nontuberculous) and 1 of which was of undetermined etiology. Cabot [2] reported a case in which there was unexplained fever of four months' duration. Necropsy revealed abdominal lymphadenopathy with ascites. The pathologic report on a lymph gland was "chronic inflammation." Christian [3] reported a case in which no cause for the general amyloidosis could be found. Shapiro [4] reported 1 case of a patient with tuberculous arthritis of both shoulders. Whitbeck [5] reported 7 cases of general amyloidosis occurring in tuberculosis of the bones. In one report it is stated that the urine contained albumin (four plus). In the others the results of urinalysis are not mentioned. He was more interested in other phases of the disease than

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From the Nicollet Clinic of Minneapolis and the Glen Lake Sanatorium, Oak Terrace.

1. Noble, J. F., and Major, S. G.: Renal Insufficiency in Amyloid Disease, Arch. Path. **8**:762 (Nov.) 1929.

2. Cabot, R. C.: Albuminuria and Unexplained Sepsis, New England J. Med. **201**:833 (Oct. 24) 1929.

3. Christian, H. A.: The Nephrosis Syndrome Associated with Idiopathic Amyloidosis, M. Clin. North America **15**:805 (Jan.) 1932.

4. Shapiro, P. F.: Lipoid Nephrosis: Pathology, Genesis and Relation to Amyloidosis, Arch. Int. Med. **46**:137 (July) 1930.

5. Whitbeck, B. H.: Liver Meal in Treatment of Amyloidosis in Surgical Tuberculosis, J. Bone & Joint Surg. **14**:85 (Jan.) 1932.

in the renal phase. Walker [6] cited a case with empyema of the lung in which the diagnosis was based on the presence of a large liver and spleen and albuminuria. The patient recovered five years after the onset. Linder, Maxwell and Green [7] reported a case following disease of the mastoid, with long continued suppuration. Bell [8] reported a case of renal amyloidosis of undetermined origin. Addis and Oliver [9] reported 5 cases under the diagnosis of the "pyogenic form of degenerative Bright's disease," 1 of which occurred in association with advanced pulmonary tuberculosis, 2 with tuberculosis of the bones and 2 with chronic osteomyelitis. Williams, who was mentioned by Holten, evidently had considerable personal experience with renal amyloidosis, but we were unable to locate his published material. In the German literature, Kieffer[10] reported 45 cases of clinical nephrosis from a tuberculosis clinic, in 42 of which it was proved at necropsy that there were amyloid deposits in the kidneys. Simon[11] reported 43 cases of nephrosis, presumably with amyloid change in the kidney, occurring in association with tuberculosis of the bones and joints and with nonpulmonary tuberculosis. In 17 of 25 fatal cases the patients were examined at necropsy, and we assume that they had proved cases. He mentions only 1 case occurring in association with other forms of tuberculosis in his experience, namely, in 1 with a case of intestinal tuberculosis with a perirectal abscess. Fahr [12] reported 10 cases, all of which showed the glomerular lesions of nephritis combined with amyloidosis of the kidneys. Two of these occurred in conjunction with tuberculosis, 4 with syphilis and 4 in patients with other infections and suppurative processes. In the Scandinavian literature, Holten [13] reported 30 cases, 3 of which were cases of hemorrhagic nephritis with amyloid disease;

6. Walker, G. F.: Case of Recovery from Amyloid Disease, Lancet **2**:120 (July 21) 1928.

7. Linder, G. C.; Maxwell, J., and Green, F. H. K.: Clinical, Pathological and Biochemical Study of Amyloid Nephrosis, Arch. Dis. Childhood **2**:220 (Aug.) 1927.

8. Bell, A. W.: Amyloid Infiltration, Journal-Lancet **42**:306 (June 15) 1922.

9. Addis, T., and Oliver, J.: The Renal Lesion in Bright's Disease, New York, Paul B. Hoeber, Inc., 1931.

10. Kieffer, O.: Kidney Disease in Pulmonary Tuberculosis, Ztschr. f. Tuberk. **33**:9, 65 and 137, 1920.

11. Simon, S.: Zur Klinik der Nephrose bei Knochen- und Gelenktuberkulose, Deutsches Arch. f. klin. Med. **163**:87, 1929.

12. Fahr, T.: Zur Frage der Nephrose, Berl. klin. Wchnschr. **55**:993, 1918; Ueber atypische Befunde aus den Kapiteln des Morbus Brightii nebst anhangsweisen Bemerkungen zur Hypertonie-frage, Virchows Arch. f. path. Anat. **248**: 323, 1924; Zur Frage der Amyloidnephrose und Amyloidschrumpfniere, Klin. Wchnschr. **10**:1205 (June 27) 1931.

13. Holten, C.: Nephritis Caused by Tuberculosis, Acta med. Scandinav. **61**:107, 1924.

4, of amyloid disease with renal tuberculosis (all these cases were proved by necropsy), and 23, of renal amyloidosis, with 18 fatal cases, in 17 of which necropsy was performed. In the French literature there are several reports of 1 and 2 cases, but no series of cases is reported. Rosenblatt [14] reported 125 cases of amyloidosis, 110 of which occurred in association with tuberculous, and 15 with nontuberculous, conditions. Of this number, 87 showed amyloid deposits in the kidney. His observations extend over 1927 to 1932, which is the same period covered by our study. Many of his findings are similar to ours, and each study corroborates many of the observations of the other. We have, however, approached the matter of diagnosis from a somewhat different angle and have been more interested in portraying the life history of the disease in the individual patient.

PATHOLOGIC AND CLINICAL DIAGNOSIS

This paper is confined to a study of 16 cases of renal amyloidosis in which a clinical diagnosis was made during life and confirmed by postmortem observation of amyloid deposits in the kidney. The presence of amyloid was considered established when demonstrated by a methyl violet stain in the microscopic sections. The hematoxylin and eosin stain and the iodine reaction in fresh and formaldehydized tissues were also utilized for its demonstration. In 4 cases (6, 11, 14 and 15) intravital staining with congo red was still present from congo red injected before death. In the last 3 cases the dye was injected four, eleven and sixteen months before death, respectively. In all the cases amyloid was demonstrated in the liver and spleen by the methyl violet stain, except in the liver in case 8.

As a result of five years' experience, we believe that if in the course of advanced pulmonary tuberculosis complicated by a suppurative process, tuberculous enteritis, tuberculosis of the serous membranes or any other major complication, or, in the course of tuberculosis of the osseous system, both albumin and casts appear in the urine in considerable amounts, a diagnosis of renal amyloidosis may be entertained with the expectation that further study will confirm it. If, associated with these changes, the liver and spleen are enlarged, the diagnosis may be considered reasonably well established.

If the liver and spleen are not enlarged, the presence of edema, normal or low blood pressure, hyposthenuria, a normal output of dye, normal nonprotein nitrogen and normal eyegrounds support the diagnosis.

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14. Rosenblatt, M. B.: Amyloidosis and Amyloid Nephrosis, Am. J. M. Sc. **86**:558 (Oct.) 1933.

If either pus cells or red blood cells are found in considerable numbers in addition to the albumin and casts, if the output of dye is diminished and nitrogen retained and if the blood pressure is elevated and the liver and spleen are enlarged, the diagnosis may be considered established, with only a slight possibility of error. On the other hand, if the liver and spleen are not enlarged, the diagnosis must be made with considerable hesitation. In this group the consideration of the clinical history, together with the clinician's experience in evaluating the many factors that may come into play, may turn the balance in favor of the diagnosis.

Proceeding in this manner, the usual acute glomerular nephritis and acute and chronic hemorrhagic nephritis may be readily differentiated, if encountered. Lipoid nephrosis and the chronic glomerular and chronic vascular types of nephritis offer greater difficulty. With these types the congo red test may be very helpful in differentiation. However, clinical experience again weighs the evidence in one direction or the other.

Looking back on our experience, especially in the cases in which a diagnosis was not made during life, we believe that in cases in which we overlooked the diagnosis we failed to suspect renal amyloidosis because we did not attach enough importance to the appearance of albuminuria and cylindruria in patients with complicated advanced tuberculosis.

SELECTION OF CASES

The following procedure was followed in the selection of cases of renal amyloidosis for study:

In the Glen Lake Sanatorium a morning specimen of urine is submitted as a routine to chemical and microscopic examination on the patient's admission and once in three months during his residence. All these reports were checked in a routine manner for albuminuria and cylindruria. When either of these was reported present, three specimens of urine were examined at weekly intervals by us. If both albuminuria and cylindruria were present in the three specimens examined, the case was considered one of probable renal amyloidosis and selected for study of the blood pressure, renal function, special physical examination and examination of the eyegrounds. The time when both albumin and casts appeared and remained more or less constant was designated as the "definite" onset of amyloidosis. If either albumin or casts appeared and remained more or less constant, we designated the time of appearance as the "presumptive" onset. Using these criteria and the routine laboratory records, we have in some cases antedated the time of the presumptive and definite onset from the time that the clinical diagnosis was actually made (table 2 and charts for cases 1 to 16). A chart showing the average specific gravity of the urine in all the cases, charts showing the results of tests in each case and photomicrographs of a section of the kidney in each case are to be found at the end of this article.

NATURE OF THE TUBERCULOSIS IN WHICH RENAL AMYLOIDOSIS OCCURS

Eleven of 16 cases (table 1) were those of far advanced pulmonary tuberculosis with cavity formation; 2, of moderately advanced pulmonary tuberculosis, 1 with cavity formation, and 3, of Pott's disease with psoas abscesses. Case 13 deserves special comment. In the beginning it was classified as a case of moderately advanced pulmonary tuberculosis. The onset previous to admission was marked by hemoptysis. Shortly afterward tubercle bacilli were found in the sputum, and after admission laryngitis developed. Carcinoma of the lung, however, completely overshadowed the tuberculosis the last two years of the illness. We believe that the carcinoma with necrosis and metastasis to bone was responsible for the deposit of amyloid.

With the exception just noted, all the patients had one or more tuberculous complications. Table 1 shows the complications noted clinically and at postmortem examination. The symbols indicate whether the diagnosis was made clinically or post mortem or clinically and confirmed post mortem. Patient 9 had the largest number, namely, eight. All told, fifty-five complications of tuberculosis occurred in the 16 patients. The most prominent complication was enteritis. In 10 cases the diagnosis was made during life, and in 2 others at autopsy only. Of the 10 patients for whom a diagnosis was made ante mortem, 3 (8, 9 and 11) showed tuberculous enteritis at autopsy; 3 (4, 10 and 15) showed amyloid infiltration in the intestine, which conceivably accounts for the clinical diagnosis, and the remaining 4 (1, 5, 12 and 14) had definite symptoms which referred to the gastro-intestinal tract and had roentgen findings which suggested tuberculous enteritis. We believe that amyloid infiltration of the intestine may produce diarrhea and other gastro-intestinal symptoms and simulate tuberculous enteritis. At least the occurrence of diarrhea and gastro-intestinal symptoms in far advanced tuberculosis should suggest the possibility of coexisting renal amyloidosis. Kieffer [10] stated that "almost all" his patients had intestinal tuberculosis. Seven other tuberculous complications occurred in the digestive tract, namely, five of the rectum and two in the appendix.

The most frequent postmortem complication was tuberculous adenitis. This was present in twelve cases, but in only 2 cases were the accessible lymph glands enlarged to the extent that a clinical diagnosis of tuberculous adenitis was made. Tuberculosis of the serous membranes forms an important group, pleurisy with effusion having occurred in 6 patients, empyema in 3, pericarditis in 4 and peritonitis in 2, involving 10 cases in all. The only other noteworthy complication is laryngitis, which occurred in 6 cases. There was confirmation at autopsy in only 1 case, but the larynx is not examined as a routine at postmortem examination at this sanatorium.

TABLE 1.—*Primary Lesions and Suppurating Focus with Complication Noted Clinically and at Autopsy, Exclusive of Amyloidosis* *

Case	Primary Diagnosis	Suppurating Focus	Tuberculous Lesions: Gastro-Intestinal Tract: Enteritis	Appendix	Rectum	Larynx	Adenitis	Serous Membrane: Pleural Effusion	Pericarditis	Tuberculous Peritonitis	Renal Complications	Other Lesions
1	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	c	..	c	c	a	..	..	..		
2	Pott's disease (ca).....	Psoas (ca)	..	..	..	..	ca	c	..	..		
3	Pott's disease (ca).....	Psoas (ca)	..	..	..	..	a	..	..	..		
4	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	c	..	..	a	a	a	..	..		
5	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	c	..	ca	..	a	..	..	..	Nontuberculous abscess (a)	
6	Far advanced pulmonary tuberculosis with cavitation (ca)	Empyema (ca)	a	a	..	..	a	ca	..	..	Tuberculous kidney (ca)	Miliary tuberculosis (a) Syphilis (c) Tubercle of heart (a)
7	Far advanced pulmonary tuberculosis (ca)	Sinuses (ca)	a	a	..	..	a	..	a	..	Tuberculous kidney (ca)	Retroperitoneal abscess (a)
8	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	ca	a	..	c	..	..	..	a		
9	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	ca	..	a	c	a	..	a	..		Tuberculous bronchiectasis (c) Otitis media (c)
10	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	c	a	ca	..	..	..	a	..	Mild chronic nephritis (ca)	
11	Far advanced pulmonary tuberculosis with cavitation (ca)	Empyema (ca)	ca	..	..	..	ca	ca	..	a	Mild chronic nephritis (ca)	
12	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	c	..	..	c	..	a	a	..	Chronic nephritis (ca)	Syphilis (c)
13	Moderately advanced pulmonary tuberculosis (c)	.....	..	..	..	c	..	..	..	..	Chronic nephritis (ca)	Carcinoma of lungs (a) Metastasis to bone (a)
14	Moderately advanced pulmonary tuberculosis with cavitation (ca)	.....	c	..	c	..	a	c	a	..	Chronic nephritis (ca)	Pancreatitis (a)
15	Pott's disease (ca).....	Psoas (ca)	c	..	..	..	a	..	..	..	Chronic nephritis (ca)	Pancreatitis (a)
16	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	..	a	..	..	a	..	..	..	Chronic nephritis (ca)	Encephalomalacia (ca) Infarct of spleen (a) Mural thrombosis of heart (a)

* c indicates clinical diagnosis; a, observation at autopsy, and ca, clinical diagnosis confirmed at autopsy. Amyloid was present in the intestinal wall in cases 4, 7, 8, 9, 10 and 15.

All but 4 of the patients showed another renal lesion. Two showed open tubercles, as diagnosed by the inoculation of guinea-pigs with urine. One patient had a terminal suppurative nontuberculous abscess of the kidney. Eight patients showed renal insufficiency (chronic nephritis), which was slight to marked on renal function tests, and which in all cases was confirmed at postmortem examination. One additional patient (9) showed postmortem evidence of chronic nephritis. The nonprotein nitrogen of the blood in this case was 29 mg. per hundred cubic centimeters three months prior to death.

PROBABLE PRECIPITATING COMPLICATION

After determination of the presumptive and definite onset of renal amyloidosis, as previously described, we were interested in trying to determine whether any unusual event in the clinical history of the patient could be associated with the renal complication. The complications that appear to stand in rather intimate relationship or coincidental with the onset of renal amyloidosis are in bold face type in table 2. The date of onset thus related is also in bold face type. In cases 1, 5, 8, 9 and 12 the evidence of renal amyloidosis occurred either with, or not longer than three months after, the onset of clinical enteritis. In case 2 the development of the psoas abscess preceded the onset by two months. Patient 3 was admitted with a draining tuberculous spine. At that time he also had a slight albuminuria. In September 1927 the abscess closed and had to be aspirated and reopened. A month later the urine showed both albuminuria and cylindruria.

In case 7 albuminuria followed tuberculous empyema after a short interval, and in cases 11 and 13 albuminuria followed pleural effusion, in the latter following the institution of pneumothorax. Patient 4 had a hemorrhage in June 1930, phreniphraxis on the left side and pneumothorax in July, and in August marked albuminuria and cylindruria. Patient 10 had slight intermittent albuminuria and cylindruria for nine years, but following thoracoplasty in May 1930 severe albuminuria and cylindruria developed. Patient 14 had cylindruria that was slight to moderate from March 1918 to November 1931. In August 1918 he had a slight albuminuria. In November 1921 he had a flareup of his tuberculosis. In December 1921 there was an abrupt onset of marked albuminuria, which persisted until death, eleven years later. Patient 16 in September 1929 showed an extension of his tuberculosis, and simultaneously a moderate number of hyaline casts appeared in the urine; October 1931 marked the onset of albuminuria.

Patient 11, who has already been mentioned, presented a remarkable feature worthy of further comment. In June 1930 purulent pleural effusion developed. The following month a moderate number of hyaline

casts appeared in the urine, which were present for four months. Repeated aspirations brought about marked clinical improvement, and the urine showed no casts for thirteen months. Then he had a high temperature and a marked spread of his tuberculosis, at which time the cylindruria reappeared and albumin was present.

TABLE 2.—*Clinical Events and Onset of Renal Amyloidosis*

Case	Clinical Events: Date	Clinical Events: Event	Date of Presumptive Onset of Renal Amyloidosis	Date of Definite Onset of Renal Amyloidosis
1	Dec. 1924	Tuberculous laryngitis	**Aug. 1925**	Aug. 1930
	July 1925	**Enteritis**		
	Jan. 1928	Ischiorectal abscess that drained		
	March 1928	Enteritis		
2	Feb. 1927	**Psoas abscess**	.....	**April 1927**
3	On admission (Dec. 1926)	Draining tuberculous spine	Dec. 1926	**Oct. 1927**
	Sept. 1927	**Abscess closed; aspirated and opened**		
4	June 1930	Hemorrhage	.....	**Aug. 1930**
	July 1930	**Phreniphraxis on the left; pneumothorax**		
5	May 1930	**Enteritis**	.....	**Aug. 1930**
6	On readmission (May 1928)	Draining empyema	May 1928	July 1928
7	On admission (Oct. 1930)	**Empyema**	**Nov. 1930**	Jan. 1931
8	Aug. 1930	**Enteritis**	.....	**Sept. 1930**
9	Oct. 1928	**Enteritis**	**Oct. 1928**	**Feb. 1929**
	Dec. 1928	**Enteritis** (second attack)		
10	Nov. 1929	Hemorrhage	.....	**May 1930**
	Feb. 1930	First stage thoracoplasty		
	March 1930	Second stage thoracoplasty		
	May 1930	**Third stage thoracoplasty**		
11	March 1930	Pleural effusion, left side	**July 1930**	**Dec. 1931**
	June 1930	**Purulent pleural effusion, right side**		
	Dec. 1931	**High fever; extension of tuberculosis**		
12	March 1927	**Enteritis**	.....	**March 1927**
13	Dec. 1927	**Pneumothorax**	.....	**Feb. 1928**
	Jan. 1928	**Fluid at base of left lung**		
14	Oct. 1921	Exercise discontinued	April 1918	**Dec. 1921**
	Nov. 1921	**Flareup of tuberculosis**		
15	On admission (July 1923)	Psoas abscess	April 1925	March 1928
	Dec. 1924	Pott's disease		
16	Sept. 1929	**Extension of tuberculosis**	**Sept. 1929**	Dec. 1931
	Jan. 1930	Bad teeth; pyorrhea		
	May 1931	Questionable enteritis and slight obstruction		

In only six cases (2, 3, 6, 7, 11 and 15) was the onset preceded by a definite suppurative complication.

The brief interval between the probable precipitating complication and the urinary observations indicating a beginning renal lesion or definite onset of renal amyloidosis is particularly striking in all but 2 cases (6 and 15). In case 6 the date of the onset of albuminuria is not known. Both these patients had a definitely suppurative complication on admission.

ALBUMINURIA

The duration of the albuminuria is shown in table 3. Slight albuminuria includes amounts that were recorded, from the smallest trace to one plus. When the results were recorded as two plus and over, the condition is called severe albuminuria. The total duration of known albuminuria varies from a minimum of three to a maximum of one hundred and seventy-one months, the average being thirty-three, and the median, from fifteen to sixteen months. The severe albuminuria was present from a minimum of one to a maximum of one hundred and thirty-one months, the average being twenty-one, and the median, from nine to twelve months.

TABLE 3.—*Albuminuria*

Case	Total Duration of Albuminuria, Months	Duration of Severe Albuminuria, Months	Comment
1	63	2	Albuminuria preceded cylindruria by 30 months
2	12	12	
3	21	3	Albuminuria preceded cylindruria by 9 months
4	12	12	Variable in amount; absent on one occasion
5	16	13	Albuminuria preceded cylindruria by 4 months
6	3 (?)	3 (?)	Tuberculous empyema developed 10 months prior to readmission, which is probable date of onset of renal complication
7	17	16	Albuminuria preceded cylindruria by 2 months
8	4	4	
9	33	6	Albuminuria preceded cylindruria by 5 months
10	4	4	
11	5	1	Cylindruria preceded albuminuria by 17 months
12	44	44	
13	11	9	
14	171	131	Cylindruria preceded albuminuria by 5 months
15	96	62	Albuminuria preceded cylindruria by 34 months
16	15	15	Cylindruria preceded albuminuria by 25 months
Average	32.94	21.06	
Median	15 to 16	9 to 12	

Patient 6 had severe albuminuria on readmission. She had had empyema ten months previously. The onset of the albuminuria probably occurred shortly thereafter, but we are including only the known period.

In 12 cases there were no urinary observations prior to the onset of renal amyloidosis to suggest any previous kidney disease. Patient 5 had a trace of albumin in December 1927, but we mark the onset of his renal amyloidosis as October 1930. Patient 10, from October 1919 to May 1930, had traces of albumin in four specimens of urine and a small number of hyaline casts in two. There was a long interval in which the results of urinalysis were negative—for more than two years before the onset of renal amyloidosis. It is likely that he had slight damage of the kidneys due to mild chronic nephritis. Patient 12 had on one occasion a trace of albumin (in August 1919), with a small number of granular casts. A small number of granular casts were noted again in

1920. The urine then remained normal until March 1927, the time of onset of renal amyloidosis. Mild acute nephritis or amyloidosis with residual damage of the kidneys at that time is a possibility. This is of interest in view of the fact that renal insufficiency developed. Patient 8 had a trace of albumin, together with slight pyuria. Neither albumin nor casts were present until a year later, when renal amyloidosis began. In 6 cases (1, 3, 5, 6, 9 and 15) albuminuria preceded cylindruria by thirty, nine, four, two, five and thirty-four months, respectively. In 3 cases (11, 14 and 16) cylindruria preceded albuminuria by seventeen, five and twenty-five months, respectively. In the other 7 cases the onset was simultaneous. Simon [11] stated that albuminuria always precedes

TABLE 4.—*Urinary Sediment*

Case	Duration of Slight Cylindruria (Few Casts to 1+), Months	Duration of Severe (2+ to 4+), Months	Variety of Cast		White Blood Cells	Red Blood Cells
			Hyaline	Granular		
1	30	2	+++	±	1+ to 4+	0
2	12	7	++	+	±	0
3	12	12	++	+	±	+
4	12	12	++	±	1+	0
5	13	11	+++	+	±	0
6	1	1	++++	—	1+ to 4+	0
7	15	15	—	+++	4+	+
8	4	4	++++	—	±	0
9	28	9	+++	±	±	0
10	4	1	+	+	±	Once*
11	22	21	+++	±	±	Once†
12	44	39	+++	±	±	0
13	11	11	++++	++	±	0
14	176	168	++++	++	2+	+
15	62	42	++++	±	3+	+
16	40	36	+++	±	1+	+
Average.....	30.4	24.4				
Median.....	13 to 15	11 to 12				

* Three months before death.
† Terminal.

cylindruria. His cases were those of tuberculosis of the bones and joints and of nonpulmonary tuberculosis.

CYLINDRURIA AND CYTOLOGY

The total duration of the cylindruria in each case is shown in table 4. Slight cylindruria was present from a minimum of one to a maximum of one hundred and seventy-six months, the average being thirty, and the median, from thirteen to fifteen months. Severe cylindruria occurred from a minimum of one to a maximum of one hundred and sixty-eight months, the average being twenty-four, and the median, from eleven to twelve months. This corresponds closely to the periods of slight and severe albuminuria. With the exception of case 7, the predominating type of cast was the hyaline variety, with from a few

to many fine droplets of fat. In a few cases typical fatty casts were seen. While we did not employ a "polarization" attachment on our microscope, we believe that one can distinguish the droplet of fat from the fine brown granule by manipulation of the light. A marked increase in the light makes the droplet of fat appear more opaque or black, while it causes the fine brown granule to become more or less invisible. This difference is more perceptible under low power than under high power magnification. The cast appears studded with black dots the size of pinpoints if droplets of fat are fairly abundant. When granular casts were present they were predominantly of the fine brown granular variety. Restriction of fluids after 6 p. m. increases the number of casts in the morning specimen.

The small round cell of the renal epithelium studded with droplets of fat and free droplets of fat were also frequently seen. In 7 cases (1, 4, 6, 7, 14, 15 and 16) pus in the sediment was present in quantity graded from one plus to four plus (one plus being from five to fifteen cells per high power field in centrifugated specimens). The first 4 patients were females, and the specimens were voided ones. Vaginal contamination is a possibility in all. Patients 10 and 11 showed red blood cells in one specimen only. Five patients (3, 7, 14, 15 and 16) more or less constantly showed a small number of red blood cells. The last 3 (14, 15 and 16) had hypertension and renal insufficiency.

In the majority of cases the urinary sediments showed the following: (1) from a few to many hyaline casts, with a varying number of fine droplets of fat; (2) a few fine brown granular casts; (3) a few white blood cells; (4) no red blood cells.

SPECIFIC GRAVITY OF THE URINE

The urinary observations just reported were on morning specimens. The sanatorium routine calls for examination of the urine once every three months. In order to obtain a normal average specific gravity, we took the first four specimens during the first year of residence of 50 consecutive living patients and of 20 patients with fatal cases in which there were no renal complications. The specimens were taken to cover every month of the year in patients in all stages of tuberculosis. The average specific gravity in 200 specimens from living patients and 80 specimens from patients with fatal cases was in both instances 1.0175 plus. We have, therefore, taken 1.018 as the average normal specific gravity of the morning specimen of urine in tuberculous patients under the sanatorium routine. Compared with this figure, the average specific gravity in our cases after the onset of renal amyloidosis is 1.014. The individual averages are shown in the chart listing the specific gravity in all the cases.

Probably the most constant and outstanding laboratory finding in these cases of renal amyloidosis is the urine of low specific gravity. In many instances the urinary pigments appear to be well excreted. The urine is dark, and the appearance suggests concentrated urine, but the specific gravity is found to be remarkably low.

Ten patients (1, 4, 5, 6, 7, 8, 11, 12, 13 and 15) showed consistently low readings for specific gravity. The last patient for eight and one half years after the onset of albuminuria did not pass a single specimen with a normal specific gravity (graphic chart for case 15). Four other patients (2, 3, 9 and 16) had only one normal specimen each of a total of thirty-two specimens examined (minimum, four specimens; maximum, eleven specimens, for individual cases). Patient 7 had two specimens with a normal specific gravity, of eight specimens examined. Patient 14 (chart for case 14) showed a specific gravity of unusual interest. For a period of four and one half years while cylindruria alone was present he secreted urine with a specific gravity at or above the normal line. For six years following the onset of albuminuria the specific gravity was at or usually below the normal line. For the last five years it was always below the normal line.

In one patient only (10) was the ability to secrete urine of normal specific gravity retained (graphic chart for case 10). This patient died of pneumonia four months after the onset of renal amyloidosis. His kidneys showed a very small amount of amyloid change. His ability to secrete urine of high specific gravity may be attributed to the small amount of damage to the medulla and to the fact that the convoluted tubules were intact. Kieffer [10] stated that the specific gravity is usually high—at times, 1.035. The highest specific gravity in our series was 1.028 on only one occasion in the last case mentioned. Our experience is in accord with Holten's,[18] who asserted that "hyposthenuria is the rule"—an observation which, according to his statement, was overlooked by Strauss and Volhard.

RENAL FUNCTION

Six patients had Volhard secretion and concentration tests. In only 1 case (13, on second examination) was the four hour output normal. Three patients showed essentially normal dilution. The ability to concentrate was impaired in all. The maximum concentration was 1.022 in case 16.

Nine patients were given the standard two hour and ten minute phenolsulphonphthalein test, with a normal result in case 2 (an output of 70 per cent) and case 13 (an output of 57.5 per cent, first test). In only 1 case was the output markedly lowered, namely in case 15 (an output of 22 per cent).

In all but 1 case (3) was the nonprotein nitrogen of the blood determined during the renal amyloidosis. Only 3 patients (12, 14 and 15) showed a significant degree of retention of nitrogen. In these the maximum nonprotein nitrogen was 174, 60 and 72 mg. per one hundred cubic centimeters of whole blood, respectively. In 2 other cases (10 and 13) the maximum figures were 43 and 46 mg., respectively. In the remaining cases the nonprotein nitrogen was normal, but in cases 4, 7, 10, 11 and 16 the interval (over three months) at which the

TABLE 5.—*Results of Renal Function Tests*

	Volhard Test			Output of Phenolsulphonphthalein in 2 Hours and 10 Minutes, Percentage	Nonprotein Nitrogen	
Case	Total 4 Hour Output, Percentage	Maximum Dilution	Maximum Concentration*		Mg.	Time Before Death
1	..	.....	.....	....	33	1 month
2	52	1.002	1.014	70.0	24	2 months
					35	1½ months
					24	½ month
3	..	.....	.....	....	..	
4	..	.....	.....	....	28	9 months
5	..	.....	.....	....	28	9 months
					31	½ month
6	..	.....	.....	45.0	33	1 week
7	..	.....	.....	40.0	34	14 months
					31	9 months
8	50	1.002	1.012	47.5	27	1½ months
9	..	.....	.....	....	29	3 months
10	..	.....	.....	....	43	5 years
11	..	.....	.....	40.0	31	16 months
12	..	.....	.....	....	39	2 years
					160	4 days
					174	1 day
13	50	1.004	1.012	57.5	29	8 months
	95	1.007	1.014	37.5	36	2 months
					46	1 month
14	64	1.002	1.021	45.0	33	6 years, 10 months
	49	1.003	1.017	40.0	34	4 years
					33	2 years, 10 months
					60	10 months
					50	7 months
15	72	1.005	1.010	22.0	41	39 months
					72	10 days
16	42	1.005	1.022	45.0	32	34 months
Normal....	80 to 100	1.001 to 1.002	1.028 to 1.032	55 to 70	30 to 35	

* Concentrations from 1.020 to 1.026 indicate moderate impairment, and those from 1.010 to 1.020, marked impairment.

nonprotein nitrogen was estimated was too long before death to enable one to state that renal insufficiency did not develop. At postmortem examination patients 10, 11, 12, 13, 14, 15 and 16 showed evidence of chronic nephritis. The results of the renal function tests are shown in table 5.

BLOOD PRESSURE

From one to several blood pressure readings were obtained in all the cases after the onset of renal amyloidosis (table 6). Normal blood pressure or hypotension was the usual finding. However, low blood pressure readings are common among our patients at the sanatorium. Patients 1 to 10, inclusive, had a low or normal blood pressure. It is

possible that hypertension may have developed in patients 4, 5 and 7 in the interval between the last reading (nine, nine and eleven and one-half

TABLE 6.—*Blood Pressure*

	On Admission			During Residence			Final Reading			
			Blood Pressure		Blood Pressure			Blood Pressure		
Case	Date	Sys-tolic	Dias-tolic	Date	Sys-tolic	Dias-tolic	Date	Sys-tolic	Dias-tolic	Time Before Death
1	Dec. 5, 1924	100	66				Aug. 1930	104	70	1 month
2	July 2, 1925			July 9, 1927	100	60	March 29, 1928	70	50	4 days
				March 16, 1928	92	80				
				March 17, 1928	118	88				
				March 19, 1928	104	90				
				March 20, 1928	112	88				
				March 21, 1928	112	88				
3	Dec. 31, 1926	104	64	.....	.....	.....	July 1928	100	66	2 months
4	Dec. 8, 1929	108	72	Sept. 1930	102	62	Oct. 30, 1930	90	70	9 months
				Oct. 16, 1930	108	70				
				Oct. 23, 1930	104	72				
5	Aug. 13, 1926	108	48	.....	.....	.....	Nov. 7, 1930	104	64	9 months
	June 7, 1929	106	50							
6	May 18, 1928	125	78	.....	.....	.....	July 26, 1928	100	60	1 day
7	Oct. 22, 1930	95	70	.....	.....	.....	March 28, 1931	102	68	11½ months
8	Aug. 21, 1929	102	66	Oct. 18, 1930	102	74	Nov. 13, 1930	108	80	2 months
				Oct. 30, 1930	100	65				
				Nov. 6, 1930	96	70				
9	June 4, 1928	110	85	.....	.....	.....	Jan. 24, 1931	108	65	3 months
10	Feb. 27, 1918	.....		April 23, 1924	110	80	May 15, 1930	118	80	3 months
				Feb. 27, 1930	104	75				
				Feb. 27, 1930	120	80				
				March 6, 1930	104	78				
				March 13, 1930	108	80				
				March 20, 1930	108	80				
11	Nov. 21, 1929	120	72	Sept. 6, 1930	138	100	Nov. 13, 1930	116	92	16 months
				Oct. 30, 1930	115	96				
				Nov. 6, 1930	126	88				
12	Aug. 30, 1924	118	74	Oct. 18, 1928	136	80	April 10, 1930	174	92	6 months
				Oct. 25, 1928	138	88				
				Nov. 1, 1928	136	76				
				March 5, 1929	128	82				
				July 19, 1929	142	82				
				April 2, 1930	180	100				
13	Dec. 26, 1925	148	90	Jan. 1, 1926	125	90	Nov. 22, 1928	135	94	1 month
				Oct. 10, 1928	134	90				
14	April 10, 1917	.....		Jan. 3, 1922	130	80	May 29, 1932	194	120	5 months
				Feb. 16, 1922	128	65				
				Dec. 29, 1925	140	98				
				Oct. 18, 1928	228	122				
				Oct. 19, 1928	226	122				
				Oct. 20, 1928	220	120				
				Oct. 16, 1929	204	130				
				March 3, 1930	194	120				
				July 3, 1930	200	130				
				Dec. 6, 1930	214	128				
				March 11, 1931	242	136				
				May 15, 1931	242	140				
				April 4, 1932	196	114				
15	July 25, 1923	108	80	Jan. 1, 1926	125	67	March 9, 1933	108	62	½ month
	Dec. 12, 1924	106	75	Oct. 10, 1928	120	78				
				Feb. 4, 1930	150	90				
				Feb. 11, 1930	146	88				
				Feb. 18, 1930	134	90				
				Dec. 6, 1932	136	74				
16	July 20, 1929	140	88	Feb. 4, 1930	162	110	Nov. 24, 1932	178	120	½ month
				Feb. 11, 1930	134	90				
				Feb. 18, 1930	154	98				

months, respectively) and death, although we do not consider it likely, since no renal vascular sclerosis was noted at autopsy. Patient 11 had a slightly elevated systolic and diastolic blood pressure in one reading and a slightly elevated diastolic and low pulse pressure in all the readings

except that taken on admission. His last reading (systolic, 116; diastolic, 92) was taken sixteen months before death. At that time the output of phenolsulphonphthalein was 40 per cent, and the nonprotein nitrogen, 31 mg. However, it is likely that a terminal rise of the blood pressure occurred, since at postmortem examination the glomerular lesion of chronic nephritis was present. Patient 12 showed a moderate grade of hypertension while under observation for renal amyloidosis. He had marked retention of nitrogen. At postmortem examination the kidneys showed arteriosclerosis and chronic nephritis. In patient 13 the condition might be termed latent hypertension. Renal amyloidosis did not appear to influence his blood pressure. He had a slight elevation of the nonprotein nitrogen one month before death. At postmortem examination the glomerular lesion of chronic nephritis was present. Patient 14 had marked and prolonged hypertension, the first evidence of which occurred four years after the onset of renal amyloidosis. Because of the high blood pressure and the good renal function as to the elimination of nitrogen during the period from eight to three years before death, we considered it highly probable that this patient had two conditions—renal amyloidosis and primary arterial hypertension. At postmortem examination marked arteriosclerosis and arteriolosclerosis and chronic nephritis were present. Patient 15 showed a slight degree of hypertension after the onset of renal amyloidosis. The blood pressure became subnormal two weeks before death. Postmortem examination showed arteriosclerosis and chronic nephritis. Patient 16 had a slightly elevated blood pressure on admission. Moderate hypertension developed. At postmortem examination arteriosclerosis and chronic nephritis were present. The 6 patients showing an elevated blood pressure were all males, and the ages at which the elevated blood pressures were first recorded were 32, 44, 46, 55, 55 and 69 years. From the evidence presented, it appears that hypertension occupies an inconspicuous position in the clinical picture of renal amyloidosis. It may be incidental rather than related to cause or effect.

EXAMINATION OF THE EYEGROUNDS

Examination of the eyegrounds was omitted in case 10. In 8 cases (1, 2, 4, 5, 6, 7, 8 and 9) the disks and retinas were normal, and there were no detectable vascular changes. Patient 3 showed a slight variation in the lumen of one inferior temporal artery. In case 13 one inferior temporal artery had a burnished appearance, suggesting early copper wire artery. In case 15 the arteries showed slight narrowing, and the choroidal vessels were slightly prominent. There was the "pepper and salt" fundus in both macular regions. In these 3 cases the vascular changes were so slight that they must be considered questionable. In

case 11 the arteries showed slight dulling of the light reflex, with slight narrowing and irregularity of the lumen. We consider these changes indicative of early retinal arteriosclerosis. Patient 12 showed slight increased vascularity of the disks, marked tortuosity of vessels, an increased light reflex (early copper wire artery) and moderate arteriovenous compression; in case 16 there were a moderately increased light reflex and irregularity of the lumen of the arteries, with slight arteriovenous compression. We consider that these 2 patients showed moderate retinal arteriolosclerosis. In case 14 the arteries showed marked irregularity and narrowing of the lumen of the arteries. Some were almost obliterated. There was slight compression at several arteriovenous crossings. This patient had marked retinal arteriolosclerosis. Retinal hemorrhages and retinitis were absent in all the patients examined. The findings just mentioned would indicate that the statements made concerning hypertension and renal amyloidosis apply also to retinal arteriolosclerosis and retinitis.

PHYSICAL FINDINGS

Certain relevant physical findings are shown in table 7.

Ten patients showed from slight to moderate pallor of the skin.

A very slight to marked edema was present in 5 cases. This was found at the time of the special physical examination, which was usually made within from one to three months after the onset of renal amyloidosis. In 2 of these cases the edema is recorded as being very slight. Edema, as noted at postmortem examination, was generalized in 6 cases. In 3 cases (12, 15 and 16) it was recorded as very slight; in 2 cases (7 and 14), as moderate, and in 1 case (2) as marked. Localized edema, particularly of the feet and hands, was slight in 3 cases (1, 3 and 8), moderate in 5 (4, 5, 6, 9 and 11) and absent in 2 (10 and 13). Simon [11] found edema in 11 of 45 cases, and initial edema was present in 6 of 30 cases observed from the beginning. He stated that in a large number of cases there is no edema present, except terminal edema. Holten [13] stated that initial edema such as that seen in ordinary nephritis is not present. In 13 of 30 of his cases there was no edema, and in only 3 cases was edema present that was not terminal. Our observations that the initial edema of ordinary nephritis is not present in renal amyloidosis are in accord with Holten's. When edema is present in the early stage of renal amyloidosis it is more insidious in its onset. One of our patients (12) had marked albuminuria for four years and at postmortem examination showed only a very slight generalized edema, and another patient (13) had severe albuminuria for nine months and no edema. We cannot find any agreement in the amount of albuminuria and edema in our series. It is possible that our patients were protected against deple-

TABLE 7.—*Physical Findings and Postmortem Weights* *

Case	Sex	Pallor	Edema		Peripheral Arterio-sclerosis	Liver		Spleen		Heart		Time of Physical Examination, Months Before Death
			Grade	Location		Cm. Below Costal Margin	Postmortem Weight, Gm.	Cm. Below Costal Margin	Postmortem Weight, Gm.	Cardio-thoracic Index	Postmortem Weight, Gm.	
1	F	2+	1+	Ankles; legs	3+	Enlarged	1,560	Enlarged	270	40	230	2
2	M	2+	3+	Legs; abdomen	1+	Not palpable	2,015	Not palpable	241	39	212	1
3	M	2+	0	..	0	3.0	3,405	0	475	35	210	4
4	F	0	0	..	0	0	2,666	0	340	41	146	12
5	M	2+	0	..	2+	8.0	3,070	0	246	40	163	10
6	F	1+	0	..	0	5.0	3,950	2	524	41	405	1
7	F	2+	2+	Face	3+	3.5	2,440	2	650	41	155	13
8	F	1+	0	..	0	3.0	2,730	0	245	34	160	3
9	F	2+	0	..	0	8.0	2,835†	6	300	41	197	6
10	M	..	..	..	..	...	1,450	..	206	38	417	..
11	M	0	0	..	3+	0	2,325	0	268	40	228	20
12	M	0	0	..	2+	0	1,967	0	108	40	588	7
13	M	0	0	..	3+	0	1,200	0	240	33	297	2
14	M	2+	2+ to 3+	Face; legs	3+	0	1,902	0	215	..	457	6
15	M	2+	1+	Legs	2+	0	2,800	4	543	43	335	42
16	M	0	0	..	2+	0	2,085	2	260	44	580	34
Average.....							2,337.5		320.7		298.8	

* The normal weight of the liver was considered to be 1,800 Gm. for males and 1,500 Gm. for females; 2,250 Gm. represents a 25 per cent increase for males, and 1,875 Gm., a 25 per cent increase for females. The normal weight of the spleen was considered to be 150 Gm. for both males and females; 270 Gm. represents an 80 per cent increase.

† Our original records show 1,835 grams as the weight of the liver in this case. As the liver is described as "firm and heavy" on gross examination, we believe that the 2 Kg. weight on the scales was misread as 1 Kg.

tion of plasma protein and edema because they were kept on a general diet with adequate protein as long as their general condition permitted.

Peripheral arteriosclerosis was an inconstant finding. When present, it could not be reconciled with other clinical features of renal amyloidosis.

The clinical estimate of the enlargement of liver and spleen, together with the postmortem weights, are given in table 7. In the 9 patients examined six months or less before death the clinician's estimate of the size of the liver and spleen was 100 per cent correct when compared with the postmortem weights. Patient 10 was not examined. In the remaining 6 patients, who were examined more than six months before death, the estimate was correct for 3. We assume that a 25 per cent increase in the size of the liver and an 80 per cent increase in the size of the spleen is necessary before enlargement of these organs can be positively established by physical diagnostic methods. These figures correspond closely with the standards of Barron and Litman,[15] who consider livers weighing 2,200 Gm. or more and spleens weighing 300 Gm. or more as hypertrophied and enlargement demonstrable by palpation. Our figures are 2,250 and 1,875 Gm., respectively, for the weight of the liver in the male and female and 270 Gm. for the weight of the spleen in both sexes, using as a basis for calculation 1,800 Gm. as the normal weight of the liver for males and 1,500 Gm. as the normal weight for females and 150 Gm. as the normal weight of the spleen for both sexes. These figures closely approximate the normal figures given by Boyd.[16]

On this basis, if enlargement of the liver had been made a requirement for a positive diagnosis of renal amyloidosis, the percentage of diagnostic error would have been 44 per cent. If enlargement of the spleen had been made a diagnostic requirement, the percentage of diagnostic error would have been 56 per cent. If the usual textbook diagnostic triad of chronic suppuration, enlarged liver and spleen and albuminuria had been insisted on, the diagnostic accuracy would have been 25 per cent. In the findings just described we have not considered the cavity of pulmonary tuberculosis as a chronic suppurating focus. On the basis of the postmortem weights, only 2 patients (10 and 13) failed to show some enlargement of the liver, and only 1 (12), enlargement of spleen.

The cardiothoracic index did not prove to be a reliable indicator of the size of the heart, when compared with the postmortem weights. This is due in part to the fact that in far advanced and fibroid tuberculosis and in patients receiving pneumothorax treatments the cardiothoracic

15. Barron, M., and Litman, A. B.: Importance of Hepatomegaly and Splenomegaly in Differential Diagnosis, Arch. Int. Med. **50**:240 (Aug.) 1932.

16. Boyd, E.: Normal Variability in Weight of the Adult Human Liver and Spleen, Arch. Path. **16**:350 (Sept.) 1933.

index is difficult to determine with accuracy. Six patients (6, 10, 12, 14, 15 and 16) had hearts above normal weight at postmortem examination (325 Gm., males; 250 Gm., females). Of these, the last 5 had renal insufficiency, and the last 4 had hypertension. Renal amyloidosis did not appear to favor cardiac enlargement in our series. In contrast, in 9 cases the heart was considerably under normal weight.

The congo red test according to the technic of Bennhold was performed in 6 cases (6, 8, 9, 11, 14 and 15).[17] The percentage of disappearance of the dye was 100, 40, 39, 90, 90 and 100, respectively. Patients 8 and 11, with a disappearance of 40 and 39 per cent, respectively (a 25 to 50 per cent doubtful range), had enlargement of both the liver and the spleen, while patient 14, with 90 per cent disappearance, had only very slight enlargement of the liver and spleen at postmortem examination (the liver weighed 1,902 Gm.; the spleen, 215 Gm.). While the congo red test is helpful in the diagnosis of amyloidosis, our experience with it in this series and in other cases leads us to believe that there is considerable variability of response. We agree with Rosenblatt [14] that in patients with chronic pulmonary tuberculosis the diagnosis of renal amyloidosis may be made with relative certainty without the congo red test. We performed the test only in cases in which the diagnosis of renal amyloidosis had been made. It is admitted, however, that in doubtful cases, such as differentiation from other types of nephritis and general amyloidosis without albuminuria and cylindruria, a positive result of the congo red test should carry considerable weight in the diagnosis.

Three patients (6, 12 and 15) had positive Wassermann reactions on admission. Patient 6 had one course of neoarsphenamine and mercury, which produced a negative serologic reaction. She showed a negative reaction on readmission in 1928. Patient 12 had a positive Wassermann reaction on second admission (no test was carried out on first admission), and it remained positive for three years. He had prolonged treatment with arsphenamine, mercury and bismuth. His serologic reaction became negative four years after the beginning of treatment. Patient 15 had two positive serologic reactions on admission. Four reactions over a seven year period were negative. In the aforementioned cases there were no clinical or postmortem evidences of syphilis. The serologic reaction in the remaining cases was negative.

PATHOLOGIC EXAMINATION

A careful search for evidence of amyloid degeneration was made in other body tissues. The tissues, in addition to gross examination with the iodine reaction, were also examined when stained by hematoxylin

17. Dr. George Fahr supplied the data for the last three cases.

and eosin and methyl violet. The distribution of amyloid in various organs as found at postmortem examination is shown in table 8. All the patients had amyloid in the kidneys, liver and spleen. In case 8 the

TABLE 8.—*Distribution of Amyloid as Noted at Postmortem Examination**

Case	Kidney	Liver	Spleen	Pancreas	Adrenals	Mesenteric Lymph Nodes	Retroperitoneal Lymph Nodes	Appendix	Tracheal Lymph Nodes	Thyroid	Small Intestine	Large Intestine
1	A	A	A	—	a	—	O	—	—	O	—	—
2	A	A	A	A	A	A	A	—	—	O	—	—
3	A	A	A	A	A	?	O	A	A	O	—	A
4	A	A	A	A	A	—	O	—	—	—	A	A
5	A	A	A	—	A	A	O	—	—	—	—	—
6	A	A	A	—	A	—	O	—	—	O	—	—
7	A	A	A	—	?	?	—	—	—	—	?	A
8	A	A	A	—	A	—	O	—	—	O	A	O
9	A	A	A	A	A	—	O	A	—	A	—	—
10	A	A	A	—	a	—	O	—	—	O	A	—
11	A	A	A	—	A	A	—	—	?	A	—	—
12	A	A	A	—	A	—	O	—	—	O	—	—
13	A	a	A	—	A	—	O	—	—	O	—	—
14	A	A	A	—	A	A	A	—	—	A	—	—
15	A	A	a	—	A	—	O	—	—	A	At	—
16	A	A	A	—	A	—	O	—	—	?	—	—
Total Cases....	— 16	— 16	— 16	— 4	— 15	— 4	— 2	— 2	— 1	— 4	— 4	— 3

* A indicates amyloid; a, a small amount of amyloid; O, no tissue examined, and —, no amyloid.
† The pylorus.

TABLE 9.—*Distribution of Amyloid and Other Lesions in the Kidney*

		Amount of Amyloid				Tubules					
		Cortex		Medulla			Suppression, with Dilatation of Those Remaining		Sclerosis		
Case	Weight of Kidney, Gm.	Glomeruli	Interstitial	Capillaries	Interstitial	Thickened Bowman's Capsule		Epithelial Degeneration	Arteries	Arterioles	Infiltration
1	234	±	—	—	+	..	..	+	..	..	—
2	515	++	+	+	±	..	+	+	..	..	—
3	213	+	+	++	+	..	+	—	..	..	—
4	268	++	±	+	±	..	..	+	..	..	—
5	242	++	±	+	+	..	..	+	..	..	+
6	427	++	+	+	—	..	++	?	..	..	+
7	848*	±	+	—	++	..	++	—	..	..	+
8	309	++	±	+	++	..	..	++	..	..	—
9	315	++++	+	++	+++	+	++	—	..	..	+
10	271	±	±	±	—	..	..	+	..	..	—
11	326	++	+	+	++++	..	+	+	..	..	—
12	276	+++	±	++	+++	++++	++	+	+	+	+
13	330	+	+	+	—	+++	++	+	++	++	+
14	415	++++	+	+++	+	+	++	+	++	++	+
15	286	++++	++	+++	+++	++++	+++	+	++	++	+
16	433	++++	+	+++	++	+	++	+	++	+	+

* Enormous tuberculous abscess of the right kidney.

liver tissue was not examined microscopically, since inadvertently no liver tissue was saved, but amyloid was demonstrated macroscopically by the iodine test. Patient 13 showed only a very small amount in the liver, and patient 15, a small amount in the spleen. All but one patient showed amyloid in the adrenals. In 7 cases amyloid was present in some

portion of the gastro-intestinal tract. The abdominal lymph nodes, pancreas and thyroid showed amyloid with considerable frequency. Our results are in close accord with those of Rosenblatt.[14]

The weights of the kidney and the microscopic distribution of amyloid are given in table 9. When the degree and duration of albuminuria and cylindruria are compared with the amount and distribution of amyloid in the kidney, it is difficult to establish any definite correlation except to state that the patients showing the smallest amount of amyloid (1, 7 and 10) were those in whom the albuminuria and cylindruria were of short duration.

SUMMARY

1. The clinical course in 16 cases of renal amyloidosis in which amyloid deposits were demonstrated in microscopic section of kidney tissue by methyl violet staining at postmortem examination is presented.

2. If albuminuria and cylindruria appear in the course of advanced pulmonary tuberculosis complicated by a suppurative process, tuberculosis of the serous membranes, enteritis or any other major complication of tuberculosis or in tuberculosis of the osseous system, the diagnosis of renal amyloidosis may be entertained, with the expectation that further study will confirm it. If, associated with these changes, the liver and spleen are enlarged, the diagnosis may be considered reasonably well established. If the liver and spleen are not enlarged, the presence of edema, normal or low blood pressure, hyposthenuria, a normal output of dye, normal nonprotein nitrogen and normal eyegrounds support the diagnosis.

3. The clinical complication of tuberculosis occurring most often in association with renal amyloidosis is clinical enteritis (10 cases). The most common complication observed post mortem is tuberculous adenitis (12 cases). Tuberculous complications involving the alimentary tract and the serous membranes form two important groups.

4. In all but 2 cases it is possible to point out an unusual event in the clinical course of the disease that may have been the precipitating complication or factor in determining the onset of the renal lesion. The most prominent events in this probable relationship are clinical enteritis, pleural effusion, empyema, the institution of pneumothorax and other surgical procedures.

5. The average duration of albuminuria was thirty-three months; the median, from fifteen to sixteen months. The average duration of severe albuminuria was twenty-one months; the median, from nine to twelve months. Albuminuria preceded cylindruria in 6 instances.

6. The average duration of cylindruria was thirty months; the median, from thirteen to fifteen months. The average duration of

severe cylindruria was twenty-four months; the median, from eleven to twelve months. Cylindruria preceded albuminuria in 3 instances.

7. In ten patients the urine showed a consistently low specific gravity. In only 1 patient was the ability to secrete urine of normal specific gravity retained. The kidneys in this case showed probably the smallest amount of amyloid deposit present in the series.

8. A diminished four hour output and impaired concentration were the most constant findings in the renal function tests.

9. Our data make it appear that hypertension occupies an inconspicuous position in the clinical picture of renal amyloidosis. It may be incidental rather than related to cause and effect. Arteriolosclerosis of the retinal vessels and retinitis occupy a similarly inconspicuous place.

10. If the usual textbook triad of the older clinicians of chronic suppuration, enlarged liver and spleen demonstrable by physical examination and albuminuria had been insisted on, the diagnostic error would have been 75 per cent.

(Charts and descriptions appear on following pages)

GRAPHIC CHARTS FOR EACH CASE SHOWING THE TIME RELATIONS OF THE VARIOUS DIAGNOSTIC TESTS

The horizontal distance represents the length of time the patient was observed from first admission to death. The blank spaces bounded by dotted lines represent the time between discharge and readmission. The horizontal distance is marked by years and half years at the bottom of the chart; age is indicated at the top.

Elements of Urinalysis.—Some of the results of single tests are represented on a time grid.

Albumin.—This was determined by a qualitative test with saturated sodium chloride and 2 per cent solution of acetic acid to eliminate mucus in the precipitate.

Specific Gravity.—The ends of the bars represent the reading of the specific gravity. The bars are extended to the 1.018 reading to show the variation around this figure as a normal.

Volhard Test.—See table 5 for the actual values. The percentage of water excreted is represented by the black bar. The ends of a cross-hatched bar above it represent the maximum and minimum specific gravity for the test.

Casts.—The number of casts are shown by the height of the bar. White bars represent hyaline casts. Cross-hatching represents granular casts. The amount of the cross-hatching represents the proportion of granular casts to hyaline casts.

White Blood Cells.—The height of the bar represents the number of white blood cells in the sediment of the urine, as explained in the text.

Red Blood Cells.—The height of the bar represents the number of red blood cells in the sediment of the urine.

Nonprotein Nitrogen.—The actual values of the nonprotein nitrogen of the blood are given in table 5. The time when the determination was made and an approximate representation of its value is given in relation to a 30 mg. guide line.

Congo Red Test.—The percentage of dye that disappeared from the blood is indicated by the height of the bar.

Blood Pressure.—The ends of the vertical black bars represent the systolic and diastolic readings. The 120 and 80 mm. lines are used as guides. Table 6 gives the actual values.

Examination of the Eyegrounds.—The time of examination of the eyegrounds is represented by the tiny square on the base line. White squares represent normal findings; black squares represent pathologic findings.

Phenolsulphonphthalein Test.—The height of the bar represents the percentage excreted in two hours. See table 5.

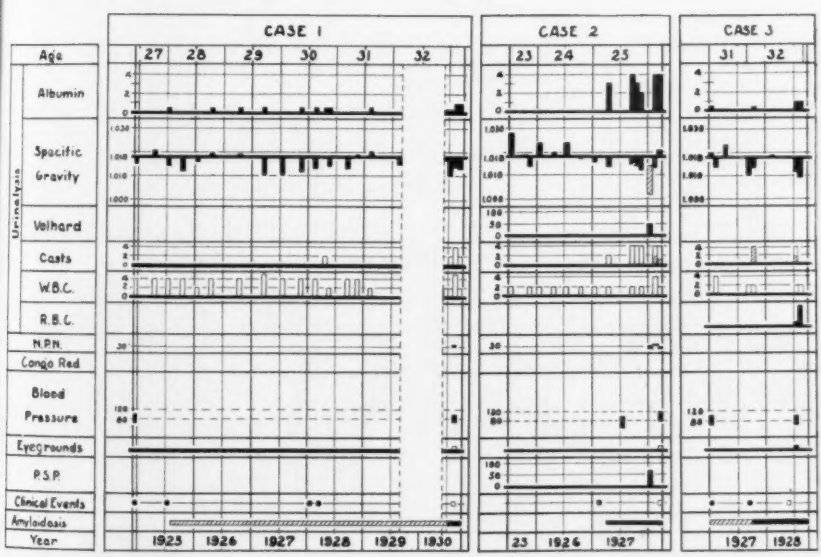
Clinical Events.—The black dots indicate the time of the various events listed in table 2. The white dots represent the time of the clinical examination for this study and the time when clinical amyloidosis was diagnosed.

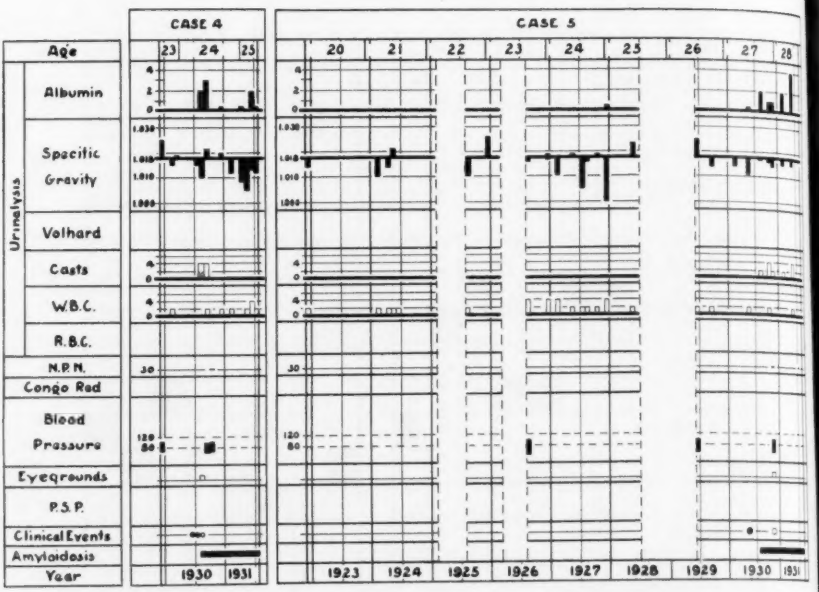
Amyloidosis.—The horizontal black bar represents the duration of clinical signs sufficiently definite to enable one to make a diagnosis of amyloidosis. It may be noted that in many of the cases the left end of the bar antedates the time when the clinical examination of the patient for this study was made. The cross-hatched bar represents the time during which amyloidosis of the kidneys was suspected but could not be definitely established.

PHOTOMICROGRAPHS

The low power photomicrographs 1 to 16 correspond to the cases so numbered. They show representative fields of amyloid in the renal cortex in each case.

Average Specific Gravity of the Urine in Individual Cases																
Specific Gravity	Case Number															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1.025																
1.024																
1.023																
1.022																
1.021										■						
1.020																
1.019																
1.018																
1.017																
1.016	■	■			■											
1.015						■										
1.014																
1.013			■	■										■		
1.012							■									■
1.011									■			■	■		■	
1.010											■					
1.009																
1.008																
1.007								■								
1.006																
1.005																
No. Specimens	4	10	6	13	7	2	7	5	12	5	4	21	15	63	31	10




CASE 4
CASE 5
Age
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Albumin
Specific Gravity
Volhard
Casts
W.B.C.
R.B.C.
N.P.N.
Congo Red
Blood Pressure
Eyegrounds
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Clinical Events
Amyloidosis
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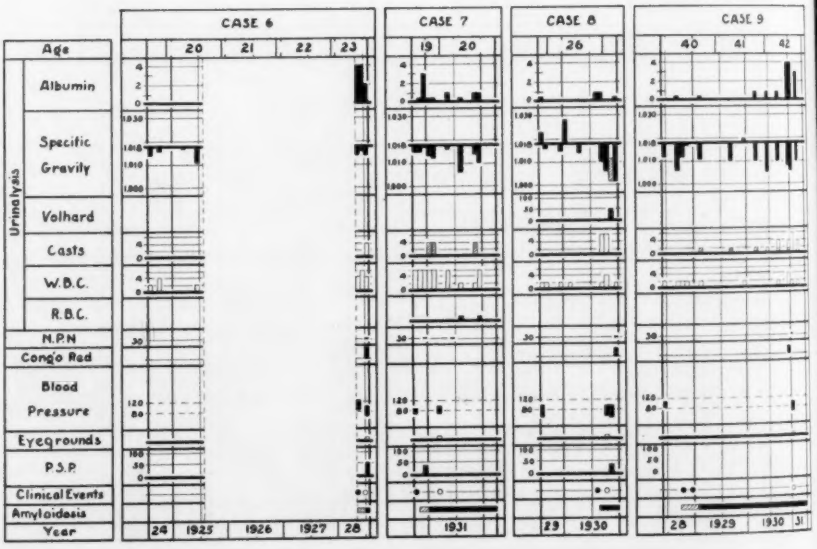
CASE 6
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CASE 9
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Specific Gravity
Volhard
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W.B.C.
R.B.C.
N.P.N
Congo Red
Blood Pressure
Eyegrounds
P.S.P.
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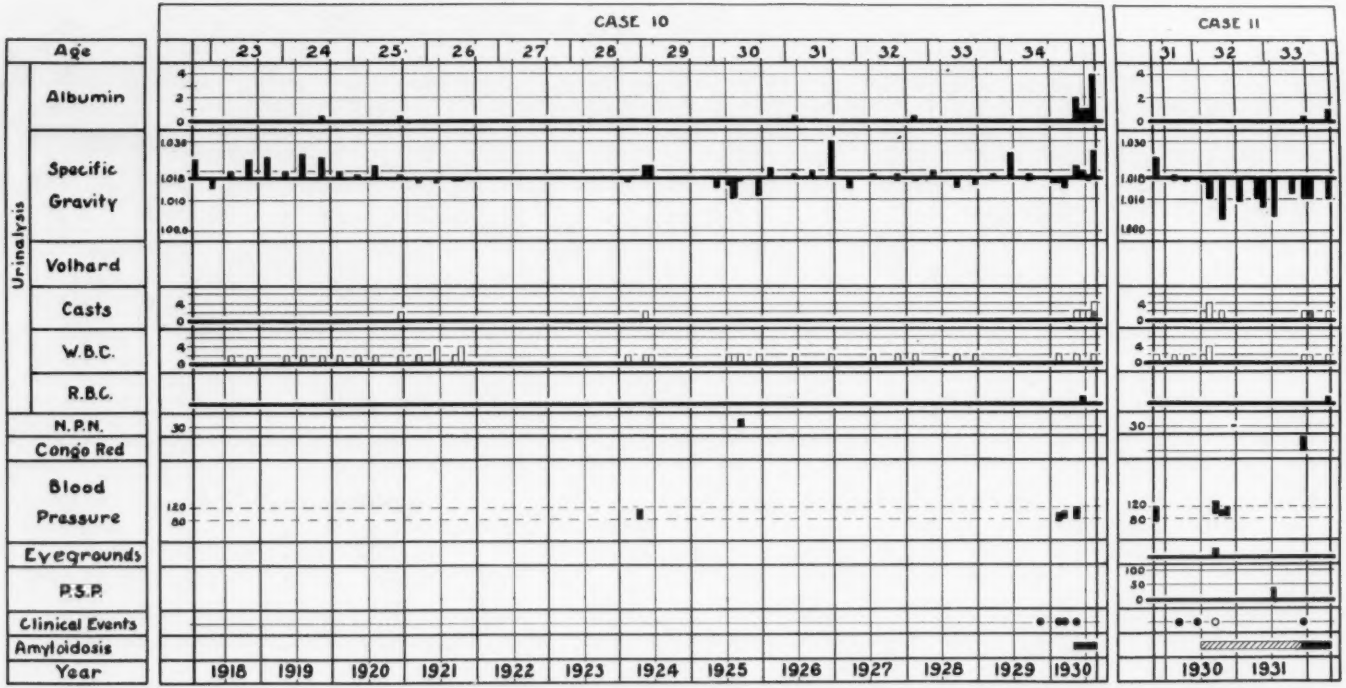
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Blood Pressure
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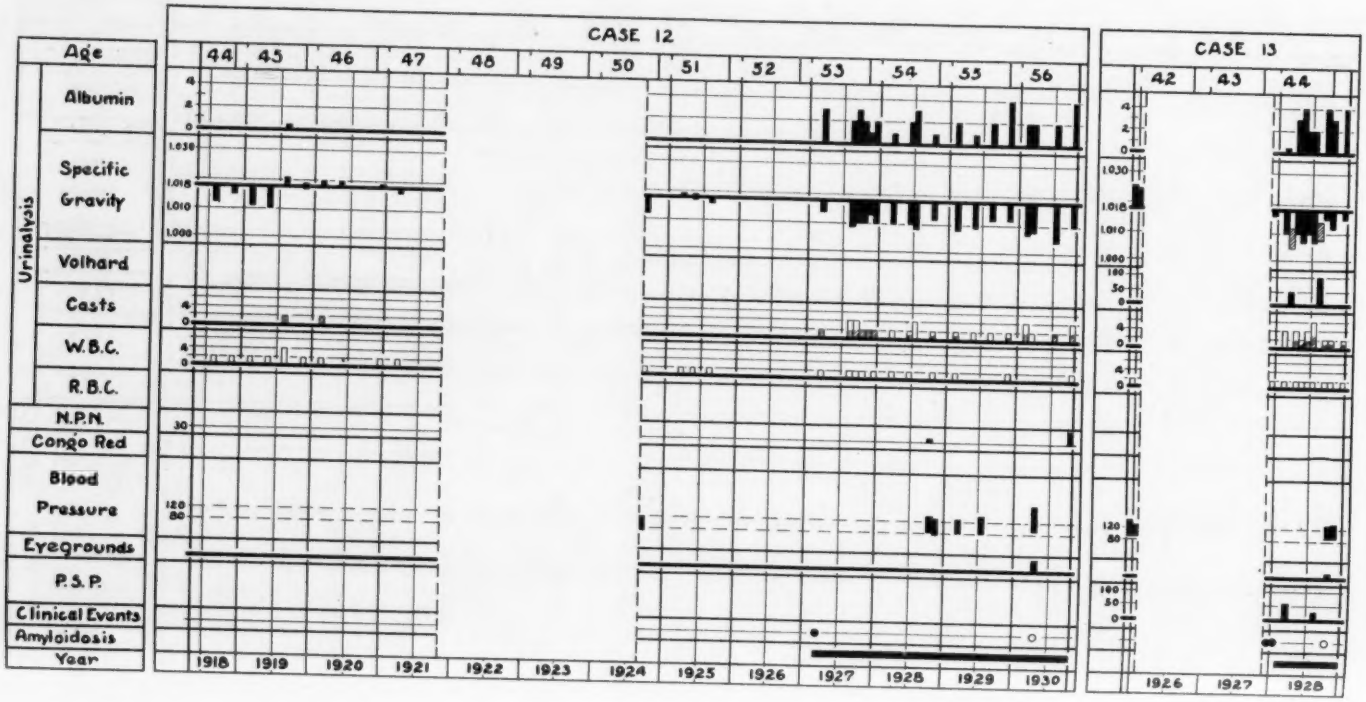
CASE 12
CASE 13
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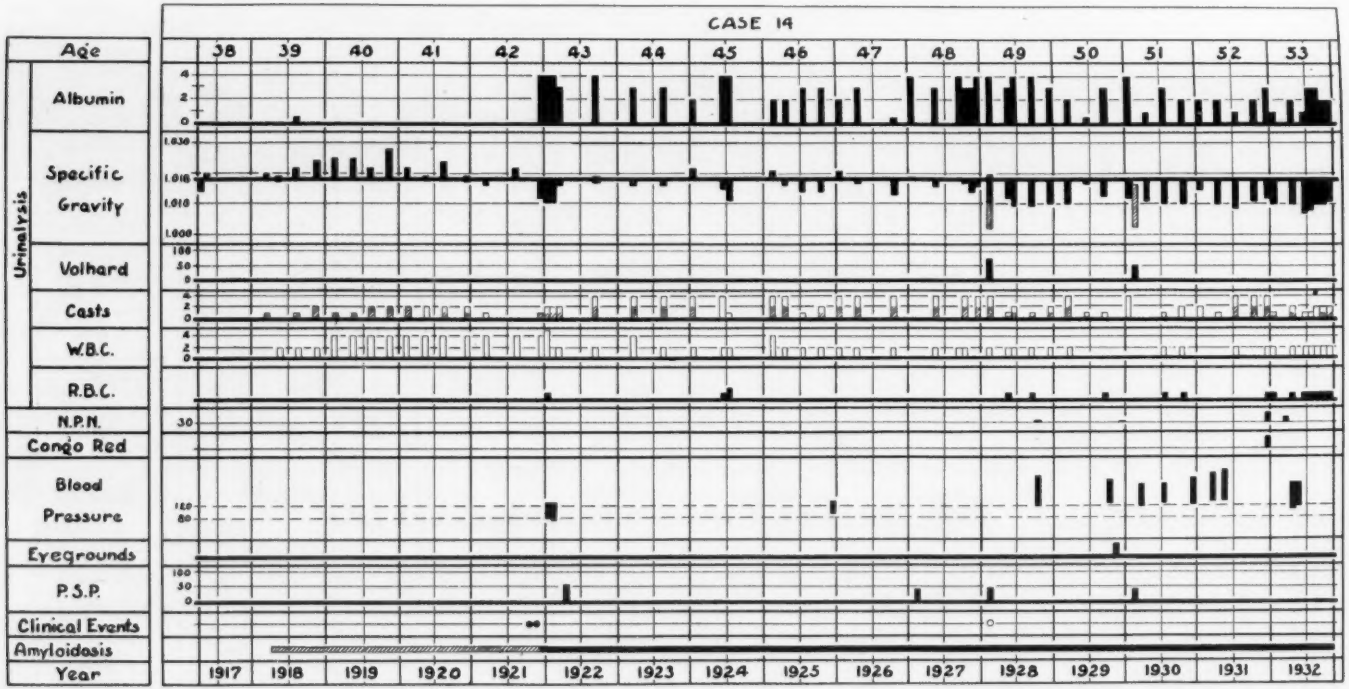
CASE 14
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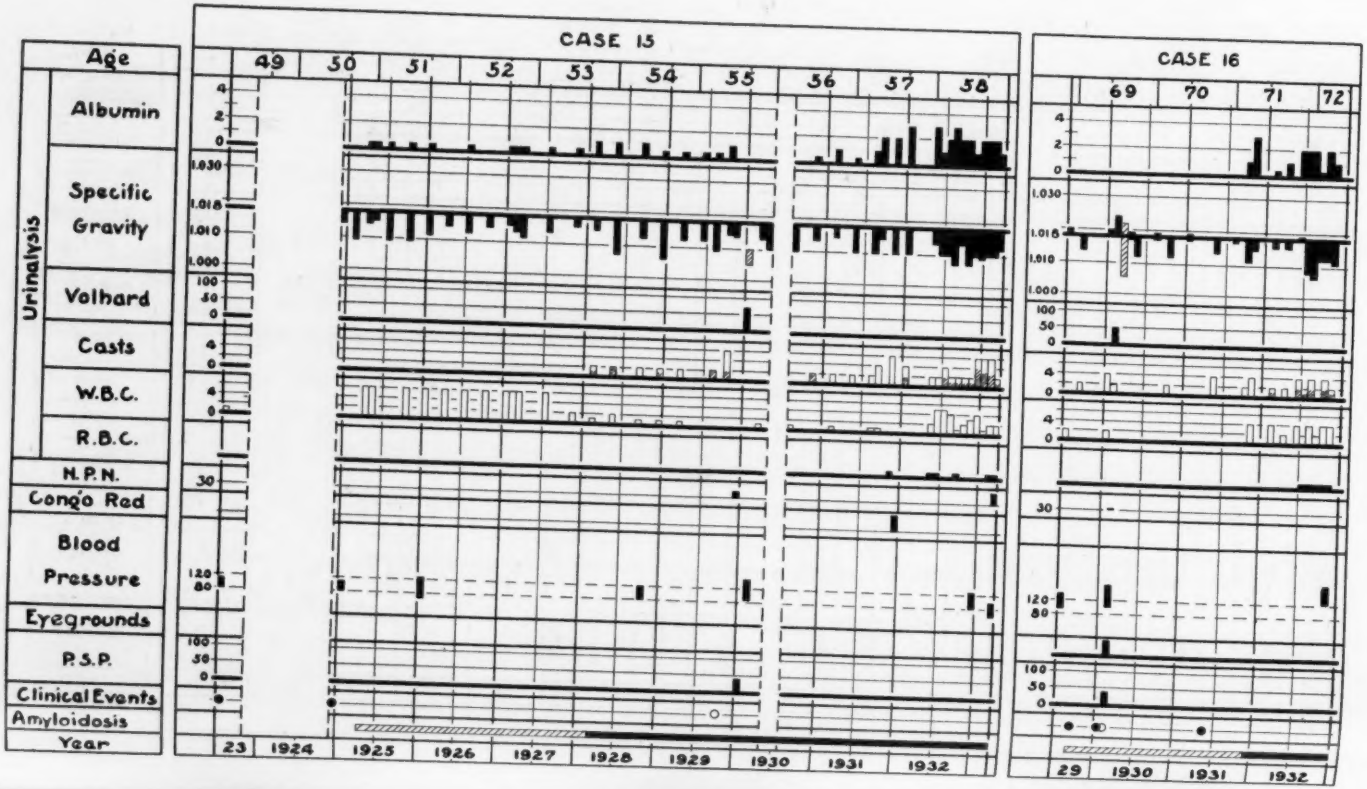
CASE 15
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R.B.C.
N.P.N.
Congo Red
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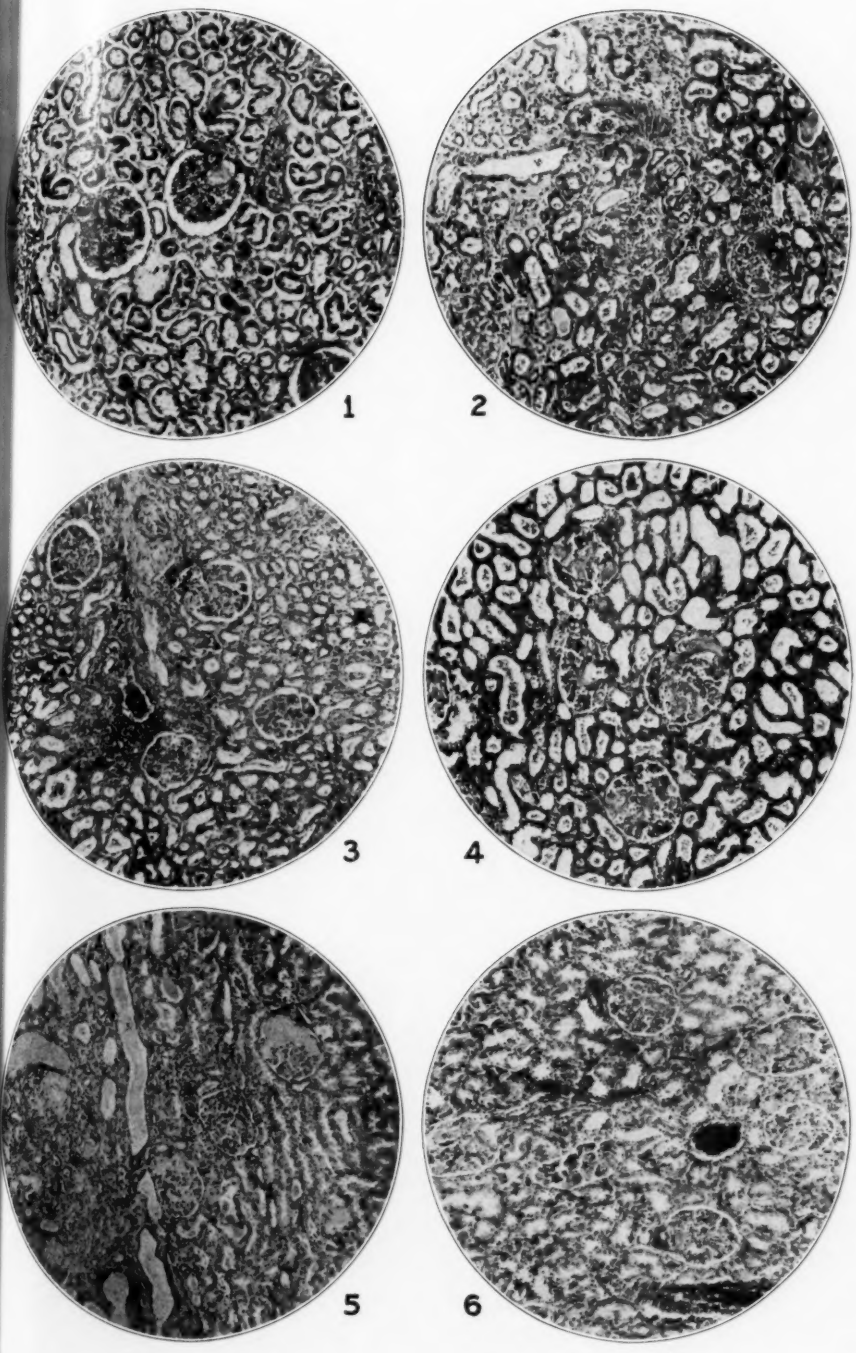
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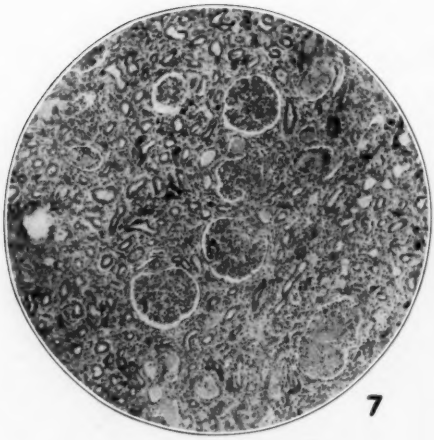

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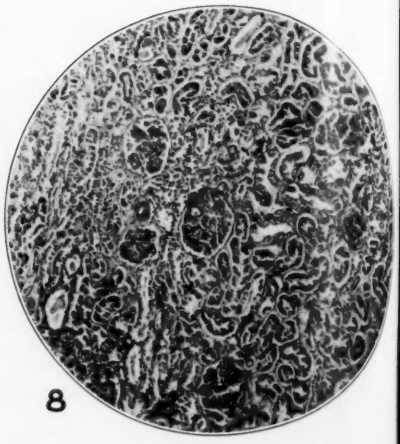

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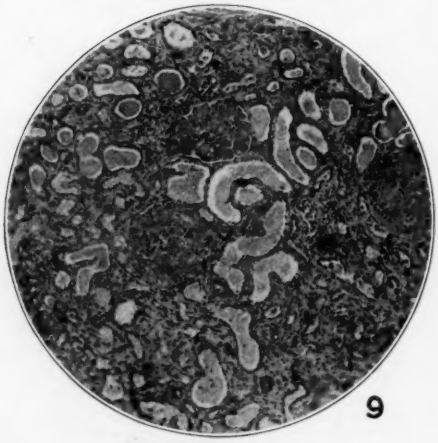

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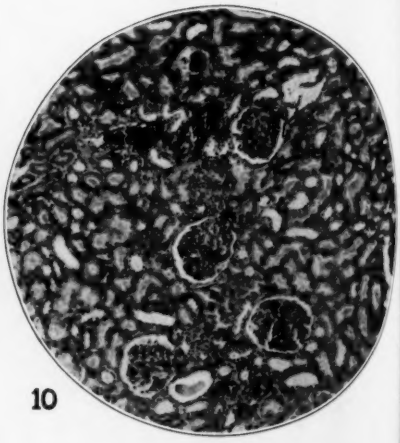

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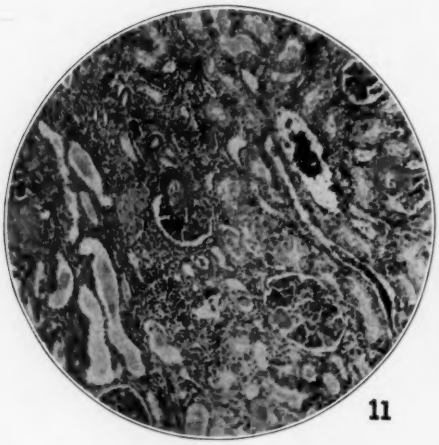

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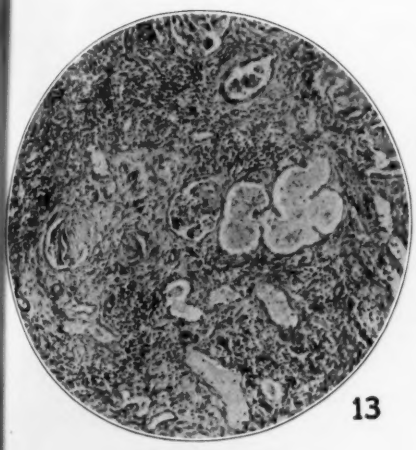

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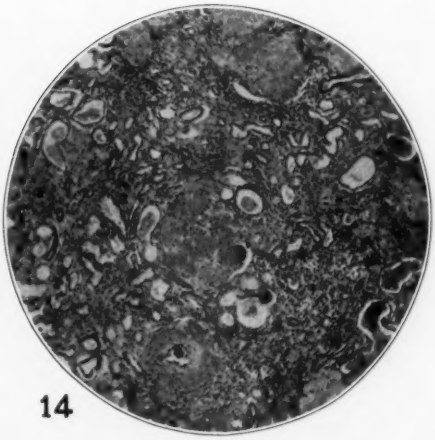

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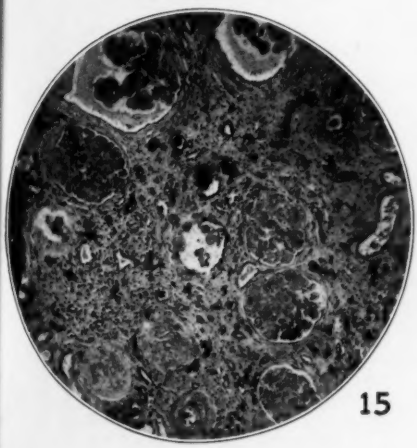

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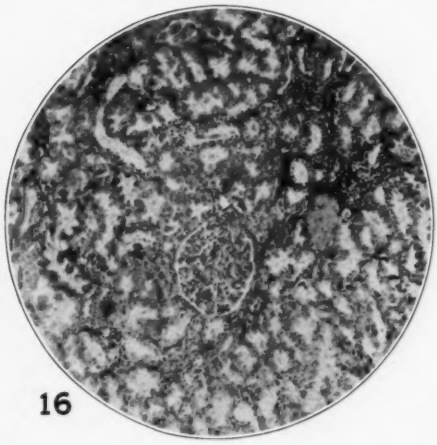

16

PATHOLOGY OF THE VESSELS OF THE PULMONARY CIRCULATION

PART IV

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BIRMINGHAM, ENGLAND

PRIMARY PULMONARY VASCULAR SCLEROSIS

In this rare condition there is sclerosis of the pulmonary arteries for no obvious reason (such as cardiac or pulmonary disease) as well as hypertrophy of the right but not the left side of the heart. Most of the patients die of heart failure. Hypertrophy of the right side of the heart, though not stressed in the definitions given in the literature, is particularly important. In the present series, 23 of 31 patients without cardiac or pulmonary disease showed pulmonary vascular sclerosis, but circulatory symptoms and hypertrophy of the right heart were present in only 1 patient, the only one in whom a diagnosis of primary sclerosis was justified. In many cases reported in the literature chronic pulmonary or cardiac disease was present or hypertrophy of the right heart was absent, so that those cases must be considered as spurious. The question may be clarified by describing 2 cases of the condition (1 of which is included among the 100 consecutive cases in the present series).

REPORT OF CASES

CASE 1.—*History and Course.*—D. D., a boy, was 11 years old at the time of death. He was apparently healthy at birth. He had an attack of influenza at the age of 3 years, and the tonsils were then removed. At 8 he had measles, the right antrum was opened and the appendix removed. At operation a condition of modified Hirschsprung disease was noted. After that there was some dyspnea on exertion with dizziness. The lips and cheeks had always been blue when the child was cold. In May 1929, at the age of 9, he had an attack of chickenpox, and after that the dyspnea and dizziness were more marked. Shortly afterward he had an attack of polio-encephalitis, with palatal and facial palsy, but recovery was satisfactory. In 1929 he had an operation for "anomalous bones in the feet." There was no history of rheumatism. He was examined at that time. The skin was pale, but the lips were bright red. The pulse rate was 90. The heart was not enlarged. There was a slight pulmonary systolic murmur, and the pulmonary second sound was accentuated. A roentgenogram showed that the heart was of normal size, with a prominent pulmonary artery. The electrocardiogram showed slight right

In this series of five papers the superior numbers refer to the bibliography which will be published in connection with the last paper. The superior letters refer to footnotes.

axis deviation. The diagnosis at that time was "effort syndrome, ? congenital cardiac disease." In the next two years he had several syncopal attacks, with drowsiness, cyanosis, muscular rigidity and incontinence, followed by vomiting. In January 1931 he had "grip" followed by otitis media and whooping cough. After that the dyspnea and tendency to cyanosis increased. Examination in June 1931, at the age of 11, revealed a good but deep color, a slightly enlarged heart and a slight harsh systolic pulmonary murmur. The pulmonary second sound was greatly accentuated and sometimes followed by a diastolic murmur. A roentgenogram showed that the heart was full-sized, with marked prominence and increased pulsation of the pulmonary artery and hilar shadows. The Wassermann reaction was negative. The electrocardiogram showed marked right axis deviation. The diagnosis was "patent ductus arteriosus, with some other defect also (?)."

In the next two months there was constantly increasing dyspnea on exertion, with slight cyanosis. Severe pain in the chest and down both arms also was felt after exertion. On Aug. 17, 1931, he had an attack of pain while being wheeled in a chair, and he died in a few minutes.

Gross Postmortem Examination.—Autopsy was limited to an examination of the thoracic organs. The body was that of a well developed and well nourished boy. There was no edema. The pleurae, thymus, bronchial lymph glands, larynx, trachea and main bronchi were normal. The lungs showed moderate congestion and edema of the lower but not the upper lobes. The pericardium was 12 cm. in transverse diameter and contained 75 cc. of serous fluid. The heart (weight, 305 Gm.) was enlarged, with marked dilatation and great hypertrophy of the right ventricle, which was 15 mm. thick at the conus and 6 mm. thick near the apex. Its columnae carneae were greatly hypertrophied. The left ventricle (fig. 21) was normal (from 9 to 12 mm. thick). The right auricle was not dilated or hypertrophied. The left auricle was small, and its wall was thin. The valves were normal apart from a patch of fatty degeneration on the aortic flap of the mitral valve. The coronary arteries showed a single small patch of early atheroma at the origin of the left main trunk. There was one patch of early atheroma in the descending aorta. Seven centimeters above the aortic cusps there was a small blind pit, proximal to which there was a fold of intima 1 cm. long and concave upward. The ductus arteriosus was closed. The stem and right and left branches of the pulmonary artery were not dilated (circumference of the stem, 5.9 cm. [aorta, 4.9 cm.]; circumferences at the hili, 3.7 cm.), but their walls were thickened, and their intima as well as that of the main intrapulmonary branches was thickened and pitted. In the branches below the second order the intima rapidly thinned and became translucent. Two small, raised, yellow, atheromatous patches were present in the stem just above the cusps, and a few similar patches were present in the branches of the first and second orders. Vessels with a diameter as small as 3 or 4 mm. stood out rigid and gaping on the cut surface of the lung. The four pulmonary veins entering the left auricle were thin-walled and narrow, their circumferences ranging from 0.9 to 2.1 cm. and the sum of their circumferences being less than, instead of (as is usual) much more than, the circumference of the stem of the pulmonary artery. There was a hemorrhage in the adventitia of the stem of the pulmonary artery extending along the left branch as far as the hilus of the lung.

Microscopic Postmortem Examination.—Microscopically the stem of the pulmonary artery showed slight sclerosis, the intima being 0.05 mm. thick. The media was thickened to 1.53 mm., and its elastic laminae were thicker and more closely set than usual. There was a great deal of well preserved extravasated blood in the adventitia.

The right and left arteries showed more marked sclerosis, the intima in places measuring 0.216 mm., but the changes were otherwise similar.

Of the intrapulmonary arteries more than 1 mm. in diameter, many were normal, but some showed marked patchy atheroma with intimal thickening, in places reaching 0.365 mm., or as much as 11 per cent of the external diameter of the vessel. The patches often had groups of fat-containing foam cells. The media and adventitia appeared normal. The most marked changes were present in the small muscular arteries, less than 1 mm. in external diameter, seventy-nine of which were carefully measured. Nineteen (diameter, from 0.078 to 0.195 mm.;

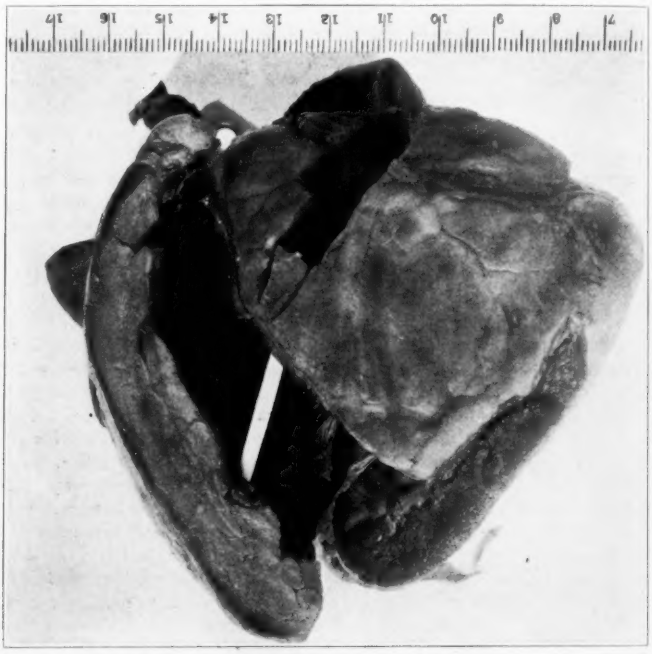

Fig. 21.—Gross appearance of the heart in case 1. The ventricles have been cut so as to show the hypertrophy of the right ventricle (on the left).

average, 0.123 mm.) of the 79 arteries were normal in all respects. Seven of the sixteen arteries less than 0.1 mm. in external diameter were normal, and one other showed only hypertrophy of the media. Seven of the twenty-six arteries between 0.1 and 0.15 mm. in diameter were normal. Five of the twenty between 0.15 and 0.3 mm. in diameter were normal. No artery between 0.3 and 1 mm. in external diameter was entirely normal. Thus, most of the small arteries that were normal were among the smallest pulmonary arteries immediately before the arterioles. Apart from the nineteen normal arteries, six showed a normal intima. Eleven showed loose connective tissue intimal thickening, staining yellowish or pink with Van Gieson's stain and showing many round and spindle cells. This was often

accompanied by proliferation of the elastic tissue or of the intimal endothelium. This change was confined to the smaller muscular arteries, occurring in one of the nineteen arteries less than 0.1 mm. in diameter (5 per cent), in four of the twenty-six between 0.1 and 0.15 mm. (15 per cent) and in six of the twenty between 0.15 and 0.3 mm. (30 per cent).

In nine arteries endarteritis obliterans was present. In all, the intima was greatly thickened and the lumen was narrowed. In four the intima consisted of closely packed rounded or polygonal cells in a scanty fibrillar stroma. In five the intima consisted of loose fibrillar connective tissue with many round and spindle cells; this differed from the change in "fibrous intimal thickening" only

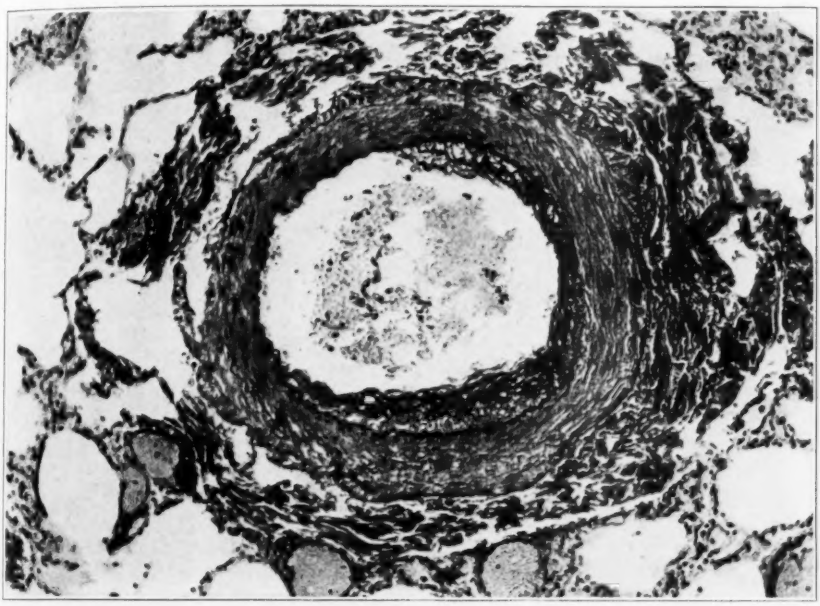

Fig. 22 (case 1).—Photomicrograph of a section of a small muscular artery (× 153; Van Gieson's stain and Verhoeff's elastic tissue stain). There is proliferation of the elastica interna and hypertrophy of the media, which is as thick as that of a systemic artery of the same size (compare with figure 3). There is a layer of longitudinally directed muscle, cut transversely, external to the circular muscle.

in the greater thickness of the intima and the greater cellularity and looseness of the connective tissue. Usually no other changes were present in the affected vessels, which varied from 0.059 to 0.137 mm. (average, 0.105 mm.) in outside diameter. This change was present in seven of the sixteen arteries less than 0.1 mm. in diameter (44 per cent) and in two of the twenty-six between 0.1 and 0.15 mm. (8 per cent). No artery over 0.15 mm. in diameter was involved. Usually no other change was present in the affected vessels.

Proliferation of the elastica interna (fig. 22) was present in fifteen arteries. In some there was only splitting of the elastica interna over part of its extent; in others there was a thick layer containing five or six thick anastomosing elastic laminae with a little connective tissue and a few round and spindle cells. The change was often patchy and especially involved points where a side branch was arising. Other changes, especially hypertrophy of the media, also were often present. The vessels were from 0.109 to 0.498 mm. (average, 0.294 mm.) in external diameter. None was less than 0.1 mm. Three of the twenty-six between 0.1 and 0.15 mm. (12 per cent) in diameter, five of the twenty between 0.15 and 0.3 mm.

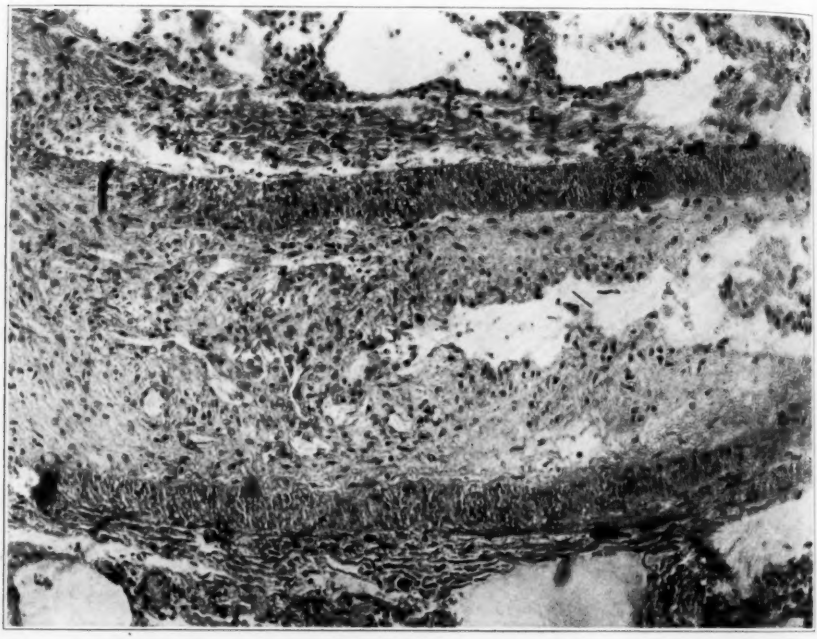

Fig. 23 (case 1).—Photomicrograph of a longitudinal section of a small muscular artery (× 160; stained with hematoxylin and eosin). There is great proliferation of the intimal endothelium.

(25 per cent) and seven of the seventeen over 0.4 mm. (42 per cent) were involved. Thus, the larger of the small muscular arteries were especially affected.

Proliferation of the intimal endothelium occurred in twenty of the seventy-nine arteries measured and was the most striking change that was observed. A great proliferation of large, round or oval cells with clear vesicular nuclei greatly narrowed or obliterated the lumen (figs. 23 and 24). There was often also fibrous intimal thickening. The diameters of the affected arteries were from 0.109 to 0.266 mm. (average, 0.163 mm.). None of the arteries less than 0.1 mm. in diameter, ten of the twenty-six between 0.1 and 0.15 mm. (39 per cent) and ten of the twenty between 0.15 and 0.3 mm. (50 per cent) were involved. Eighteen of the twenty arteries with endothelial proliferation were between 0.11 and 0.21 mm. in

external diameter, and eighteen of the thirty-seven arteries of this size (50 per cent) were involved. The strictness with which the changes were confined to vessels of this size was remarkable (fig. 24). Often an artery of 0.4 mm. in diameter with hypertrophy of the media and proliferation of the elastic tissue gave rise to a branch with a diameter of from 0.16 to 0.18 mm., the lumen of which was almost blocked by endothelial proliferation. These might divide into branches with a diameter of from 0.07 to 0.1 mm., which were normal in all respects.

Hypertrophy of the media (fig. 22) was noted in thirty of the seventy-nine muscular arteries measured, the external diameter being from 0.06 to 0.913 mm.

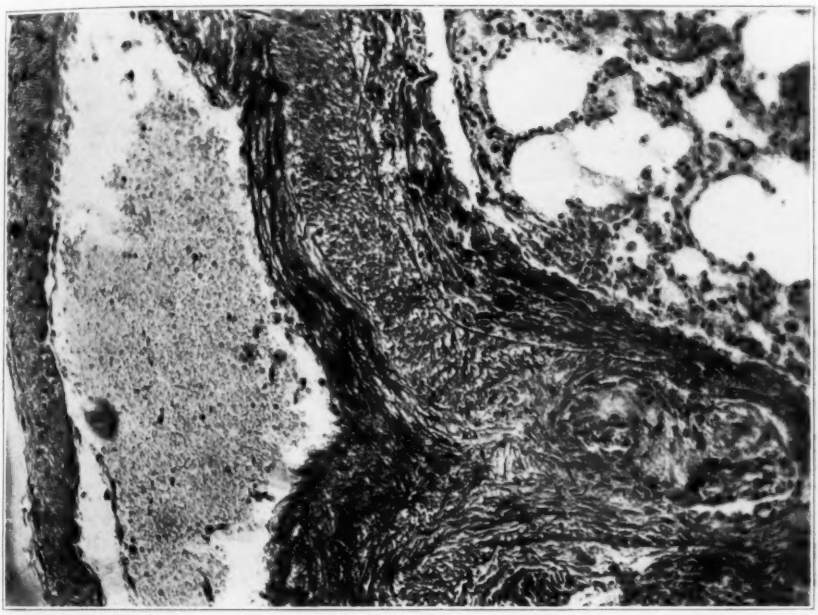

Fig. 24 (case 1).—Photomicrograph showing the distribution of lesions (× 188; stained with Van Gieson's stain and Weigert's elastic tissue stain). To the left is an artery with an external diameter of approximately 0.36 mm. and with a hypertrophied media and proliferated elastica interna, but without endothelial proliferation. To the right is a branch of this artery approximately 0.17 mm. in external diameter, with a media of normal thickness and with the lumen almost obliterated by proliferated endothelium.

One of the sixteen arteries less than 0.1 mm. (6 per cent) in external diameter, four of the twenty-six between 0.1 and 0.15 mm. (15 per cent), eight of the twenty between 0.15 and 0.3 mm. (40 per cent) and all seventeen arteries over 0.3 mm. were involved. Thus, the larger of the small muscular arteries were chiefly involved. The media was heavy and muscular, resembling that of systemic vessels, and sometimes made up 30 per cent of the external diameter. its thickness being

equal to the diameter of the lumen. A little fine irregular elastic tissue was present among the muscle fibers. There was always a complete or incomplete layer of longitudinal muscle outside the normal circular muscle, and this sometimes made up a third of the total thickness of the media, sometimes being separated from the rest of the media by a fine elastic fiber. Sometimes there was also an incomplete layer of longitudinal muscle immediately beneath the internal elastic lamina.

The adventitia of many of the muscular arteries was thick and dense and showed foci of round cell infiltration. The arterioles and venules (fig. 22) were almost all normal, though a few showed slight endothelial proliferation. The small and large intrapulmonary and extrapulmonary pulmonary veins showed no abnormality. The aorta showed slight early atheroma. Some of the vasa vasorum of the stem of the pulmonary artery and some of the small bronchial arteries showed a thick layer of longitudinal muscle fibers outside the normal circular muscle of the media.

A branch of the coronary artery, 0.78 mm. in external diameter, showed a thickened media, the inner portion of which contained a great deal of homogeneous material which stained pink with Van Gieson's stain and pale blue with methylene blue and eosin, separating and distorting the muscle fibers. The adventitia was very thick and dense and contained a great deal of irregular elastic tissue and some longitudinal muscle. The appearance somewhat suggested that of a healed inflammatory lesion of the wall of the artery.

The heart showed a little perivascular fibrosis with a few lymphocytes and large mononuclears. No Aschoff bodies were seen.

Case 2.—*History and Course.*—A woman, aged 27 at the time of her death in 1929, had been "mentally weak," and the history she gave was unreliable. She had never been strong. She had measles and mumps in childhood and influenza in 1918. In January 1923, fifteen months before her first admission, she had bronchitis with a cough and a great deal of sputum; she once spat up a little blood. Since then she had been dyspneic on exertion and was subject to cough with expectoration. There was an indefinite history of syphilis in her father.

At her first admission in April 1924 the temperature and the pulse and respiratory rates were normal. She looked well, and there was no cyanosis. There was a slight lumbodorsal scoliosis. The heart was somewhat enlarged, especially in the third left space, where the border of the cardiac dulness was 6 cm. from the midline. There was a pulmonary systolic murmur, and the pulmonary second sound was greatly accentuated. The spleen was palpable. The roentgenogram showed "a mediastinal shadow of unusual shape, increased in size in the region of the pulmonary artery, which had a definite pulsation." The electrocardiogram showed slight right axis deviation. The Wassermann reaction was negative on two occasions. The provisional diagnosis was congenital cardiac disease.

The patient was readmitted in January 1929 with an attack of bronchopneumonia of two days' duration, previous to which she had been well since leaving the hospital. The temperature ranged from 100 to 104.6 F., the pulse rate from 120 to 160 and the respiratory rate from 27 to 35. She was slightly cyanosed and extremely dyspneic. The left border of the cardiac dulness in the fifth space was 3 cm. outside the midclavicular line. There was marked dulness in the area of the pulmonary artery, with a slight continuous thrill, a short rough systolic and a longer blowing diastolic murmur there and to the right of the sternum. The pulmonary second sound was greatly accentuated. There were dulness and râles at the base of each lung. The liver was palpable. There was slight edema of the legs. The roentgenogram showed a greatly enlarged heart with marked promi-

nence in the region of the pulmonary arterial conus. The Wassermann reaction was negative. The clinical diagnosis was congenital cardiac disease with bronchopneumonia.

Gross Postmortem Examination.—Autopsy showed a fairly well nourished and well developed young woman with no edema. The liver was slightly smaller than usual and showed three or four depressed stellate scars. Otherwise the abdomen and its contents appeared normal. The right pleura showed slight, and the left extensive, adhesions. There was a thick purulent exudate in the trachea and bronchi, completely filling the small bronchi. The lungs showed many bronchopneumonic patches. Blood vessels were prominent on the cut surfaces. The pericardium contained 250 cc. of clear yellowish fluid. The heart was not weighed. It was greatly enlarged (15 cm. in transverse diameter). The right ventricle was dilated and markedly hypertrophied (11 mm. thick, compared with 13 mm. for the left ventricle). The left side of the heart appeared normal. The valves were normal, and there were no congenital defects. The aorta showed evidence of slight early atheroma. Its circumference was 5.5 cm. The pulmonary artery was greatly dilated (circumference, 13 cm.). The branches also were dilated. There was no constriction or obstruction. There were many small, scattered, raised, yellowish atheromatous patches in the stem and main branches. The pulmonary veins were not measured.

Microscopic Postmortem Examination.—Microscopically the stem of the pulmonary artery showed diffuse intimal thickening, with round and oval cells and clumps of fat-containing foam cells. In the depths of the intima there was a great deal of delicate elastic tissue and longitudinal muscle. The media and adventitia appeared normal. Many large intrapulmonary arteries showed similar changes. Others showed only slight intimal thickening, and others were normal. Many small muscular arteries were normal, but some showed fibrous intimal thickening, slight or marked, with narrowing of the lumen. The fibrous tissue was sometimes dense and hyaline and sometimes loose and cellular. In some the intima contained capillary lumens. A few arteries were blocked by dense fibrous tissue, with recanalization by small capillaries. The venules and small veins were greatly dilated and engorged. No large veins appeared in the sections. The lung tissue showed great congestion and acute bronchopneumonia. There were no chronic inflammatory or fibrotic lesions.

Comment.—Although deformities of the chest wall and pleural adhesions are both sometimes regarded as possible causes of secondary pulmonary vascular sclerosis, the changes in the second case were so slight that it seems unlikely that they had any influence.

It should be noted that the histologic changes in the two cases were different. In case 1 there was great endothelial proliferation and sometimes fibrous intimal thickening, with marked narrowing of the lumen. The hypertrophy of the media in the large muscular arteries and the atherosclerotic changes in the large elastic arteries were perhaps secondary to this. In case 2 the changes were those of ordinary atherosclerosis and were no greater than in many cases in which heart failure was not present and the right ventricle was of normal thickness. The review of the literature which follows shows that several different lesions have been reported under the name primary pulmonary vascular sclerosis.

INCIDENCE

Primary pulmonary vascular sclerosis is a rare condition. Moschowitz [212] and Turnbull (quoted by Konstam [150]) expressed a disbelief in its existence. MacCallum [187] found 1 case in 12,000 autopsies, and in that case slight emphysema was present. Reports of 66 cases have been found, in addition to the 2 previously described, but not more than 16, including case 1, described here, can be accepted without reserve. The others showed some factor, such as chronic cardiac or pulmonary disease, that was thought capable of causing secondary sclerosis either in severe form or, as in case 2, so mildly that it was improbable that it had any bearing on the condition. In others there was no autopsy or the description recorded was incomplete.

Sex.—Of the 68 patients, 36 were males and 32 were females.

Age.—The age varied from 6 weeks to 74 years, but most of the cases occurred in childhood, adolescence and early adult life.

MACROSCOPIC APPEARANCE

In order to justify a diagnosis of primary pulmonary vascular sclerosis all the factors commonly (though perhaps erroneously) thought to cause secondary pulmonary vascular sclerosis must be absent, and there must be marked hypertrophy of the right ventricle. Some authors have said that there should also be no systemic vascular sclerosis, though others have said that this is not necessary, and indeed the presence of a few fatty flecks in the intima of the systemic vessels is so common as scarcely to be considered pathologic. Finally, the changes in the pulmonary vessels must not be due to a specific infection, such as syphilis or rheumatism, though obviously inflammatory changes are not excluded as long as their origin is uncertain. The following 16 cases (some of them not well described) are the only ones that meet these requirements: case 1 described here, the cases of Tschistowitsch,[300] Sanders,[264] Bryant,[50] Ljungdahl,[176] Kuntschik,[153] and Schütte [275]; the 2 cases each of Goedel,[117] Hart [131] and Krutsch;[151] and 1 case each of Eppinger's 5,[98] Mönckeberg's 2,[208] Rössle's 2 [252] and Ulrich's [302] 2 cases.

Heart.—The right side of the heart, especially the ventricle, was always enlarged and in many cases was said to be enormously hypertrophied and dilated. The right ventricle was from 5 to 14 mm. thick and sometimes, as in case 1, was thicker at the conus than at the apex. The left side of the heart was normal or atrophied and often looked like a mere appendage of the right, which usually formed the apex of the heart. An excess of pericardial fluid, never more than 200 cc., was present in several cases, including case 1. A great excess, such as Rogers [254] noted in his cases in Indians (the descriptions of which are

not sufficiently detailed for them to be accepted without reserve as cases of primary sclerosis) and which he said was associated with great dilatation of the coronary sinus, was not noted in these cases.

Pulmonary Vascular System.—The main pulmonary veins were narrow in case 1, in Ljungdahl's case and in Krutsch's first case. The aorta was narrow in these same cases. Macroscopic changes in the pulmonary arteries were often slight, and in the cases of Eppinger, Schütte and Tschistowitsch they were absent. Moderate dilatation of the stem and main branches was present in case 1 and in 5 other cases. In many cases there were a few slightly raised whitish or yellowish patches or streaks in the intima of the stem and main branches, usually more marked in the branches of the second order and smaller and sometimes confined there. In Ljungdahl's case, which is unique, there was great thickening of the intima of the stem and main branches, with narrowing of the lumen. The changes, even microscopically, were less in the small branches. Thickening and rigidity of the smaller vessels, which projected open and gaping from the cut surface of the lung, were present in case 1 and in 7 other cases.

A partly organized thrombus occluded the right main pulmonary artery in Hart's first case. In Goedel's first case a large, fairly well organized thrombus partly occluded the stem of the pulmonary artery and spread to the right main branch and its branches, some of which were completely occluded. In Goedel's second case some medium-sized arteries were occluded by thrombi.

Lungs.—Pleural effusions were present in 3 cases (blood-stained in Schütte's cases). Eppinger said that the lungs, in contrast to the congestion of the other organs, were anemic and that the absence of clinical evidence of pulmonary congestion is an important point in the diagnosis of primary sclerosis. The lungs were anemic in 4 cases, including Eppinger's, but in 4 others they were markedly congested and edematous. In case 1 there was moderate congestion of the lower lobes. Thus, the fact that the obstruction to the pulmonary circulation lies on the arterial side of the capillaries does not always prevent the occurrence of pulmonary congestion.

A recent infarct of the lung was found in only 1 case.

Miscellaneous.—The organs other than the lungs usually showed chronic venous congestion. Great ascites was present in the cases of Ljungdahl and Schütte. The systemic vessels showed marked changes only in Bryant's case, though in case 1 and in some others there was a slight fatty change in the aortic intima.

MICROSCOPIC APPEARANCE

Microscopically several different lesions were described. In Ljungdahl's case there was enormous intimal thickening, reaching 1.44 mm. in

the stem and main branches of the pulmonary artery. The thickened intima consisted of loose connective tissue with round and oval cells and masses of fat. The small and medium-sized arteries were normal. This case is unique, though Ljundahl himself later described a case in which there was a similar distribution of the lesions, which he then ascribed to organization of thrombi. In all the other cases the changes were much more marked in the small than in the large arteries, which in 7 cases, including case 1, showed only moderate atherosclerosis. In the other cases the large vessels either were normal or were not described.

In the small arteries there was fibrous intimal thickening, sometimes with few and sometimes with many cells. In the cases in which there were few cells there was usually a great deal of fine elastic tissue, and in the cases in which there were many cells and the change appeared to be inflammatory there was little or none. In all cases some of the vessels escaped, and in some (e.g., Schütte's) the changes were localized to only one part of the lungs. A few vessels were obliterated, and many were said to be greatly narrowed, though in some the pictures purporting to illustrate this showed what has been considered in the present investigation as only a moderate degree of sclerosis. In no other case were there the great endothelial proliferation, proliferation of the elastica interna and hypertrophy of the media shown in case 1. In a series of cases which are probably examples of primary sclerosis, though slight lesions of the lungs were also present, Bredt [42] found the chief lesion to be a peculiar fibrinoid necrosis of the media of the small vessels, with infiltration of red blood cells and sometimes aneurysmal dilatation. In some cases there was also reactive intimal thickening, though Bredt thought the lesion of the media was primary.

It is, therefore, obvious that primary sclerosis is not a pathologic entity but that several different conditions are included under the same name.

SYMPTOMS

The symptoms were chiefly those of failure of the right ventricle, for which no adequate cause can be found. Dyspnea was characteristically slight, and there was usually no orthopnea. This, in many cases, was in striking contrast to the severity of the cyanosis and edema. Cyanosis was usually intense, often deeper than any that is commonly seen except in cases of congenital cardiac disease, but in case 1 and in Ljungdahl's case, cyanosis was present only on exertion, and in 2 cases cyanosis was not mentioned. Polycythemia was often associated with the cyanosis, but sometimes it was not marked and, as in case 1, the red cell count was normal.

Edema was often even more prominent than cyanosis and was sometimes the leading symptom, being associated with ascites and pleural

effusions. In Ljungdahl's case (and also in Mattirole's,[195] in which the lungs were not normal, so that it is not included among the definite cases) ascites was the first symptom, and the clinical diagnosis was cirrhosis of the liver. In 6 cases, including case 1, edema was not present.

Palpitation was common, but was rarely troublesome.

Hypercyanotic angina occurred only in case 1, and there it was atypical in that there was no mention of an intensification of the cyanosis and that the pain radiated down the arms instead of deep into the chest.

Blood streaking of the sputum occurred in 1 case.

Nervous symptoms, such as somnolence, vertigo and syncope, sometimes developed, but were pronounced only in case 1, in which for 2 years there were attacks of syncope, with drowsiness and cyanosis, accompanied by muscular rigidity and incontinence and followed by vomiting.

Examination showed no physical signs of chronic pulmonary disease, though pleural effusions sometimes occurred as part of a general anasarca. Eppinger stressed the absence of evidence of congestion of the lungs, though in some of the cases reported there were crepitations at the bases.

The heart was usually slightly enlarged to the right or to the right and the left. The pulmonary second sound was usually greatly accentuated and in 3 cases, including case 1, it was followed by a soft diastolic murmur due to functional incompetence of the pulmonary artery. There was often a soft pulmonary and apical systolic murmur but no evidence of organic valvular disease. The pulse was usually small, regular and fairly rapid and the blood pressure was normal. The electrocardiogram, when mentioned, showed only right axis deviation, which in case 1 increased in degree over a period of two years. Roentgenograms showed a slightly enlarged heart with a prominent pulmonary artery and right ventricular conus, but with a normal left auricle in the oblique view. Eppinger stressed the absence of evidence of pulmonary congestion. Excessive pulsation of the hilar shadows was noted in some cases of functional pulmonary incompetence.

The duration of symptoms varied from five months to five years, the average being less than two years. The course was steadily downhill, and treatment was ineffective.

DIAGNOSIS

In typical cases it is possible to diagnose the condition. The chief points are: (1) severe cyanosis and edema, with comparatively little dyspnea (though as in case 1, cyanosis may be slight and edema absent); (2) clinical and electrocardiographic evidence of hypertrophy of the

right ventricle but not of the left; (3) an accentuated pulmonary second sound, perhaps with a pulmonary diastolic murmur, without murmurs indicative of valvular or congenital cardiac disease; (4) no clinical or roentgenographic evidence of chronic pulmonary disease; (5) roentgenographic evidence of enlargement of the right heart with prominence of the pulmonary artery and conus of the right ventricle, but with a normal shadow of the left auricle, and (6) no evidence of syphilis.

When mistakes have been made, the case was usually regarded as one of mitral stenosis or congenital cardiac disease, though occasionally the diagnosis of adherent pericardium with Pick's syndrome was made.

PATHOGENESIS

A. Nature of the Vascular Changes.—In some cases, both typical and with slight disease of the lungs, the change appeared to be inflammatory, with cellular connective tissue thickening of the intima and sometimes [r] with scanty round cell infiltration of the media and adventitia. In others the primary change appeared to be due to hyaline degeneration of the walls of the small vessels ascribed to typhus infection [157] or a peculiar necrosis of the media [42] due to some unknown toxin. In case 1 the cellular intimal thickening and the great endothelial proliferation (resembling that seen in a more localized form in cases of acute rheumatism) were probably due to the action of bacterial toxins, while the hypertrophy of the media and the hyperplasia of the elastic tissue in the somewhat larger arteries were probably secondary.

However, in most cases the changes appeared to be those of ordinary atherosclerosis and to be noninflammatory. Though it is agreed that in the systemic circulation hypertension is at the most a contributory factor in the development of atherosclerosis, most authors have suggested that primary sclerosis is caused by pulmonary vascular hypertension, due either to spasm of the pulmonary arterioles (which, since they consist merely of an endothelial tube surrounded by an elastic fibril with no muscle, is unlikely though not impossible) or to a congenital narrowness of the main pulmonary veins, such as has been described in a few cases, including case 1, in which case marked chronic venous congestion of the lungs would be expected. This is usually not the case. The narrowness of the pulmonary veins is probably an effect and not the cause of the diminished blood flow through the lungs. Some authors have suggested that an important factor is congenital inferiority of the pulmonary artery, which makes it unable to withstand the normal pulmonary arterial pressure. The resulting arterial lesions increase the blood pressure and so set up a vicious circle. There is no evidence to support this view.

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Benda [27] suggested that the condition may be identical with thromboangiitis obliterans, but the pathologic lesions are different. In cases in which thrombosis was a marked feature, such as those of Goedel, it was suggested that possibly a large embolus had broken up and become disseminated throughout the lungs, where it then organized.

Thus in a small group the cause is probably an unknown infection. In another small group possibly widespread embolism with organization is responsible. But in most, the cause is unknown.

B. Relationship of the Arterial Lesions to Hypertrophy of the Right Ventricle.—Most authors have assumed that the changes in the pulmonary arteries cause a marked rise in the pulmonary arterial pressure and hypertrophy of the right ventricle due to overwork. But doubts arise when the question is investigated closely. In all cases some vessels were normal. In some cases, such as case 2, the vascular changes were only moderate. Much more marked arteriosclerosis occurs without hypertrophy of the right ventricle. In some of the cases that have been reported the vascular changes were trivial. Ulrich [302] described a case of primary sclerosis and another case in which almost identical symptoms and equally great hypertrophy of the right ventricle were noted at autopsy, with normal pulmonary vessels even on microscopic examination. It is generally agreed that in the systemic circulation the most extreme arteriosclerosis does not cause hypertension. According to reports in the literature,[s] ligation of the pulmonary artery to one lung causes only a slight and transient rise of the pulmonary arterial pressure and a scarcely perceptible hypertrophy of the right ventricle even after many months. Multiple embolism of the smallest arterial branches in goats, to an extent causing death in a few hours,[87] causes only transient changes in the pressure in the right ventricle. This is because of the great reserve of small pulmonary vessels and their distensibility. On the other hand, Schmidt [271] has described a case of multiple embolization of the pulmonary vessels by tumor in which most of the small arteries were occluded by clumps of tumor cells with secondary thrombosis. The patient died of heart failure, and at autopsy hypertrophy of the right ventricle was manifest. It is impossible to deny that the hypertrophy and heart failure in this case were due to the obstruction of the pulmonary circulation, which, however, was more marked than in the cases of primary sclerosis that have been reported, as most of the small arteries were occluded and not merely narrowed. On the whole, therefore, it seems unlikely that the hypertrophy of the right ventricle and the heart failure are directly due to the lesions in the pulmonary vessels, since similar symptoms and hypertrophy of the right heart may occur without pulmonary vascular lesions, and lesions

(*s*) 81, 266, 268, 303.

greater than those in many of the cases that have been reported may occur without hypertrophy of the right ventricle or symptoms of heart failure. It should be remembered, as stressed by Lewis,[171] that all the facts about ventricular hypertrophy are not yet known, and there is a great deal of evidence that it need not necessarily be due to overwork. It is possible that the pulmonary vascular lesions and the ventricular hypertrophy and failure are due to some unknown common cause rather than that they are related as cause and effect.

C. Symptoms.—The symptoms were those of failure of the right heart, with chronic venous congestion of the organs and edema. The slightness of the dyspnea was due to the absence of great congestion of the lungs, so that the vital capacity was not so diminished as in ordinary cases of heart failure. The cyanosis, which was a striking feature in many cases, is difficult to explain. Oxygenation of the blood occurs not in the small arteries, which are diseased, but in the capillaries, which are normal and through which the blood flow is if anything slower than normal, so that more time is given for gaseous exchange. No adequate explanation of the cyanosis has yet been offered. The hypercyanotic angina which occurred in some cases is also difficult to explain. It has been suggested that the pain was due to stretching of the sclerotic large pulmonary arteries by the rise in blood pressure during exertion. But the large arteries were often only slightly sclerotic or not at all, and the belief that ordinary angina is due to stretching of the aorta has practically been abandoned. It seems possible to reconcile hypercyanotic angina with the current theory that angina is due to myocardial anoxemia and so to make it a special type of ordinary angina. The cyanosis which was present in these cases was associated with imperfect oxygenation of the arterial blood and thus with a chronic myocardial anoxemia. During exercise the cyanosis, and therefore the myocardial anoxemia, increased, and the demand of the myocardium for oxygen increased. Pain therefore arose. It should be noted that in case 1, which was the only undoubted case of primary sclerosis in which cardiac pain occurred, there was a lesion of the coronary artery, with narrowing of the lumen, which no doubt diminished the supply of the impoverished blood to the myocardium.

Thus, the subject of primary pulmonary vascular sclerosis raises many problems of pathology and pathologic physiology which still await solution.

ENDARTERITIS OBLITERANS OF THE PULMONARY VESSELS

There is growing doubt as to the desirability of retaining the name endarteritis obliterans. By it is meant great thickening of inflammatory type of the intima of small arteries together with great narrowing or

obliteration of the lumen. The thickened intima consists of cellular connective tissue with lymphocytes and perhaps a few polymorphonuclears. There may be a few capillary lumens and some irregular elastic fibrils. A similar picture may result from the organization of thrombi or as a reaction to injury of the vessel wall or even physiologically as a result of disuse, as in the ductus arteriosus after birth or the uterine arteries after parturition. It is also difficult to distinguish it from ordinary arteriosclerosis of small arteries without lipoid deposition, since the intima may be cellular in degenerative and acellular in inflammatory cases.

In the pulmonary arteries endarteritis obliterans has been described in connection with chronic pneumonia, which was thought to be due possibly to rheumatism in a woman with mitral stenosis,[43] in connection with anthracotic nodules in a patient who died of heart failure secondary to chronic pulmonary disease [226] and in connection with what the authors thought (usually without adequate evidence) to be syphilitic disease of the pulmonary vessels.[t]

In the present series, changes in the small muscular arteries, which for the sake of convenience were called endarteritis obliterans, were present in 12 cases. There were two types of lesions. In the first there was pronounced and uniform connective tissue thickening of the intima with narrowing or even obliteration of the lumen. The connective tissue was sometimes dense but usually loose and cellular, with many fibroblasts and lymphocytes, some large mononuclears and in 2 cases a few polymorphonuclears. In 1 case a few multinucleated giant cells were present in the intima near foci of fibrocaseous tuberculosis, and in 2 cases there were a few capillary lumens. The 9 patients with this type of lesion were as follows: 1. A patient (case 1) with primary sclerosis, previously described. 2. A child of 13 months with a chronic pulmonary abscess. All the affected arteries were near the abscess. 3, 4 and 5. Three persons with chronic fibrocaseous tuberculosis. The affected arteries were all near tuberculous foci. 6. A woman with bronchiectasis. The affected vessels were all near dilated and inflamed bronchi. 7. A woman with hypertension. 8 and 9. Two men with emphysema and fibrosis of the lungs. In the last 3 cases no connection could be traced between the arterial changes and a local chronic inflammatory lesion, but in 1 case the changes seemed to be related to deposits of secondary growth in the perivascular lymphatic vessels. In no case was the change widespread enough to cause any material obstruction to the pulmonary circulation.

The second type of lesion (fig. 25) was found in 4 cases (in the case of primary sclerosis both types occurred). There was great

(*t*) 125, 231, 248.

intimal thickening, sometimes with obliteration of the lumen. The intima consisted of closely packed oval or polygonal cells with small central vesicular nuclei, separated from each other only by a delicate network of fine fibrils, which stained pink with Van Gieson's stain. At first glance such a vessel in transverse section looked like a nerve, the clear cytoplasm of the intimal cells with their well defined cell boundaries looking like the neurilemma and the space left after dissolving away the myelin sheath, while the nucleus looked like the axis cylinder. If a lumen was present at all, it was usually small and

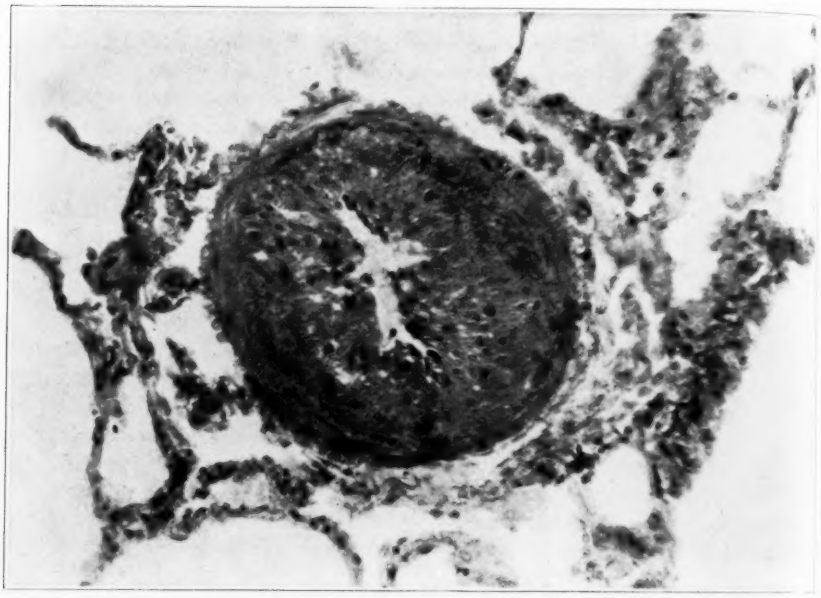

Fig. 25.—Photomicrograph of a section of a small muscular artery showing endarteritis obliterans (× 260; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). The greatly thickened intima consists of closely packed polygonal cells in a scanty fibrillar stroma. The lumen is considerably narrowed.

eccentric. Immediately beneath the endothelium was a fine, often fragmented elastic fibril. Sometimes there were one or more similar fibrils concentric to the lumen, between this and the internal elastic lamina, which was much thicker. In addition, a few irregular elastic fibrils were sometimes present in the intima. Only a few vessels in each case were affected. They often lay in thick strands of connective tissue, apparently representing interlobular septums, but occasionally they were noted in the parenchyma of the lung. Similar changes were more com-

monly seen in the bronchial arteries and the vasa vasorum of the pulmonary vessels. These changes were seen in the following patients: (1) A patient (case 1) with primary sclerosis; (2) a woman of 33 with chronic nephritis and hypertension; (3) a boy of 11 with rheumatic cardiac disease, and (4) a woman of 77 with coronary arterial disease and emphysema. There seemed to be no connection between this type of lesion and a local chronic inflammatory lesion, and too few vessels were involved to obstruct the pulmonary circulation seriously.

The two types of lesion are thus distinct. The first type is probably a reaction to local irritation, especially an inflammatory irritation. The second is of obscure origin. Neither type is of any clinical importance.

HYPERPLASIA OF THE INTIMAL ELASTIC TISSUE

Hyperplasia of the elastic tissue of the intima is common in the systemic circulation, especially in the small renal arteries, where it is almost constant in some degree in elderly persons and is greatly increased in patients with hypertension. The elastica interna thickens and then splits into two parts, with a layer of connective tissue between. This may be repeated, so that five or six thick elastic laminae, more or less parallel to each other but sometimes anastomosing, may be formed, separated by a little connective tissue. The change occurs in the muscular arteries of the heart, brain, viscera and limbs and elsewhere but is always most advanced in the kidneys. The lesions are most marked in cases of hypertension, but the fact that they are always most advanced in the kidneys makes it unlikely that hypertension alone is the cause. Possibly the functional strain on the renal vessels resulting from the large volume of blood flowing through them makes them more susceptible to high blood pressure.

In the pulmonary circulation (figs. 22 and 26) elastic hyperplasia is much less common. Arrillaga [9] said that it occurs in Ayerza's disease. Steinberg [285] described it in the arterioles in 1 of his cases of primary sclerosis, and isolated cases have been described in cases of mitral stenosis.[u] In the present series, elastic hyperplasia was present in only 3 patients: (1) a man of 52 with hypertension and congestive heart failure, (2) a woman of 26 with mitral stenosis and heart failure (fig. 26) and (3) a boy of 11 with primary sclerosis and congestive heart failure (fig. 22). Only the small muscular arteries were involved. In the first 2 cases only a few arteries were affected; in the last about 20 per cent of the small muscular arteries and 40 per cent of those over 0.3 mm. in diameter were involved. There were from three to six intimal elastic laminae, more or less parallel but anastomosing to some extent, each about as thick as the elastica interna. Sometimes the whole

(u) 43, 161, 306.

circumference of the artery was not involved, and the change was then most marked near the origin of the branches.

Congestive heart failure was present in all 3 cases, and the right ventricle was markedly hypertrophied (from 6 to 15 mm. in thickness) in all. It is therefore probable that pulmonary vascular hypertension was present, thus supporting the view that the change is a reaction to mechanical strain on the wall of the vessel due to hypertension.

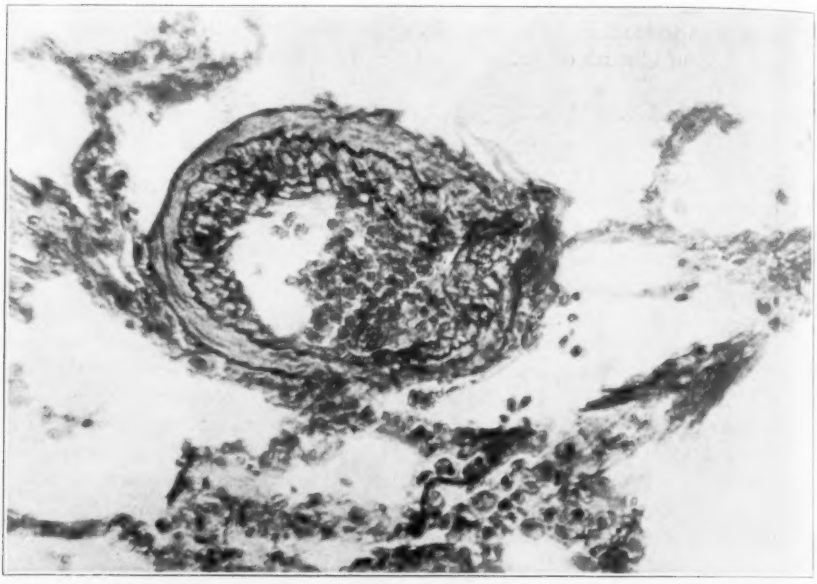

Fig. 26.—Photomicrograph of a section of a small muscular artery from a patient with mitral stenosis, showing elastic tissue hyperplasia (× 347; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). The elastica interna is split into from two to four layers with a little connective tissue between.

PROLIFERATION OF THE INTIMAL ENDOTHELIUM

Proliferation of the intimal endothelial tissue is rare apart from that which occurs in connection with organizing thrombi. Gordon[118] described a case of subacute pulmonary arteritis in a case of congenital cardiac disease. The walls of the arterioles were infiltrated with round cells, and their lumens were filled with desquamated proliferated endothelium. In the present series endothelial proliferation was found in the following three patients aside from those in whom it was part of the organization of thrombi: 1. A woman of 34 with many pyemic abscesses in the lungs. Many of the arterioles, venules and small veins

near the abscesses were plugged by desquamated proliferated endothelial cells with one or more nuclei. Some showed phagocytosis of the red blood cells. The neighboring lymph glands also showed marked proliferation of the endothelium of their sinuses. 2. A woman of 26 with mitral stenosis and recent rheumatic endocarditis (see section on rheumatism of the pulmonary vessels). Several large elastic intrapulmonary arteries showed large masses of rounded or spindle-shaped endothelial cells projecting into the lumen. 3. A boy of 11 with primary pulmonary vascular sclerosis in whom about half of the smallest pulmonary arteries were involved. It is probable that in all three cases the change was related to infection. Only in the case of primary sclerosis were the changes widespread enough for the question of obstruction of the pulmonary circulation to be raised.

HYPERTROPHY OF THE MEDIA

The relationship of hypertrophy of the media to hypertension is unsettled, partly because of the difficulty of being sure how far postmortem measurements correspond to the actual thickness of the media during life. Jores [138] said that the media may be either thicker or thinner than normal in cases of hypertension. Rossiter [258] and others held that in diastole the muscle of the media actively contracts on the receding column of blood, thus helping to propel it ("the peripheral heart"), and that in cases of hypertension the force of this contraction increases resulting in time in hypertrophy of the media. Eliaschewitz [94] described a case of mitral stenosis without hypertrophy of the right ventricle but with marked thickening of the media of the small pulmonary arteries. He believed that the contraction of the arteries was able to drive the blood through the narrow mitral orifice, thus making hypertrophy of the right ventricle unnecessary. But in this case practically all the muscle in the thickened small arteries was longitudinal, with only a thin outer layer of circular muscle corresponding to the normal media. It is difficult to see how longitudinal muscle could by its contraction narrow the arteries and so drive on the blood.

Hypertrophy of the media of the small pulmonary arteries is described in isolated cases of mitral stenosis,[v] in a case of patent ductus arteriosus [118] and in cases of chronic pulmonary disease.[w] Campbell [51] observed marked hypertrophy of the media of the small pulmonary arteries in cats kept for long periods under low oxygen pressures.

In the present series the media of the stem of the pulmonary artery, but not of the large intrapulmonary elastic arteries or of the small muscular arteries, was slightly thickened in cases of congestive heart

(*v*) 43, 306, 331.
(*w*) 221, 256, 331.

failure, in which the pulmonary vascular pressure might be expected to be high. But in the small muscular arteries in cases of congestive heart failure the average thickness of the media was 12 per cent of the external diameter, or a little less than the average normal thickness. Marked thickening of the media of the small arteries was noted in only 2 cases. One woman of 33 had chronic nephritis and hypertension and hypertrophy of the right ventricle (8 mm.) as well as hypertrophy of the left heart. A few arteries showed a thick media consisting of cir-

Fig. 27.—Photomicrograph of a transverse section of the stem of a pulmonary artery (× 238; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). To the left is shown the outer part of the media and to the right, the inner part of the adventitia with a vas vasorum. Its media consists of a thin inner layer of circular muscle cut longitudinally and a much thicker outer layer of longitudinal muscle cut transversely.

cular muscle with a little fibrous tissue, but in most of the arteries the media was normal. In the patient (case 1) with primary sclerosis previously described (fig. 22), all the muscular arteries of more than 0.3 mm. in external diameter (i. e., those larger than the arteries showing endothelial hyperplasia) showed a thick muscular media, consisting chiefly of circular muscle but with a layer of longitudinal muscle outside this. It is possible that the hypertrophy of the media in this

case was due to the narrowing by endothelial hyperplasia of the smallest muscular arteries, though it is difficult to see why longitudinal muscle should also be present.

While hypertrophy of the media was rare in the pulmonary vessels, it was common in the vasa vasorum of the stem of the pulmonary artery (fig. 27) and to a less extent in the bronchial arteries and the vasa vasorum of the large intrapulmonary vessels. This change was found in the vasa of the stem in 28 cases, in the bronchial arteries in 7 and in the vasa of the intrapulmonary vessels in 2. The intima was usually normal, though it sometimes showed any variety of disease. Outside of it was a layer of circular muscle about the thickness of the normal media, and outside of that was a layer of longitudinal muscle, up to four times the thickness of the circular muscle, sometimes divided into bundles by delicate strands of connective tissue. A few elastic fibrils were also present, and sometimes the outer layer was separated from the inner circular layer by a delicate elastic fibril. In the earliest stages of this change, the outer longitudinal layer was incomplete, typically forming in transverse section symmetrical triangular heaps of muscle cells cut transversely, with the base of the triangle applied to the circular muscle, at opposite poles of the cross-section of the artery. In 3 cases there was a great deal of fibrosis of the inner circular layer, which was replaced by dense connective tissue containing only the remnants of muscle, and in 1 case the external longitudinal layer was similarly fibrosed.

This change was present in the vasa and bronchial arteries in all the etiologic groups, in both sexes and at all ages, including the case of a child of 13 months. Usually only a few vessels in each case were involved. Jores [138] said that a little longitudinal muscle normally occurs in the adventitia, and that it is abnormal only when it is in great excess. Whether this statement has any bearing on the changes previously described, in which the outer layer of longitudinal muscle seemed to be part of the media, is difficult to say.

FIBROSIS OF THE MEDIA

Little has been written on the subject of fibrosis of the media, though Bell [26] said that in elderly patients replacement by fibrous tissue of atrophic muscle in the small muscular systemic arteries is common.

In the small muscular pulmonary arteries the media normally contains no connective tissue, so that the presence of connective tissue, which stains pink with Van Gieson's stain, is abnormal. Fibrosis was present in 33 of the present series (31 per cent of the males and 36 per cent of the females). In 29 cases the change appeared to be degenerative. Patches of muscle were replaced by dense hyaline connective tissue (fig. 28). The change never involved the whole thickness or the

whole circumference of the media, though in several cases the medial fibrous tissue was continuous through gaps in the internal or external elastic membrane with that of the intima or adventitia.

The fibrosis seemed to be inflammatory in origin in 4 patients: 1. A man of 43 with syphilis of the aorta and pulmonary artery. The media of some of the larger muscular arteries was completely replaced over part of the circumference by dense fibrous tissue. The internal and external elastic laminae were both absent, and small vessels grew

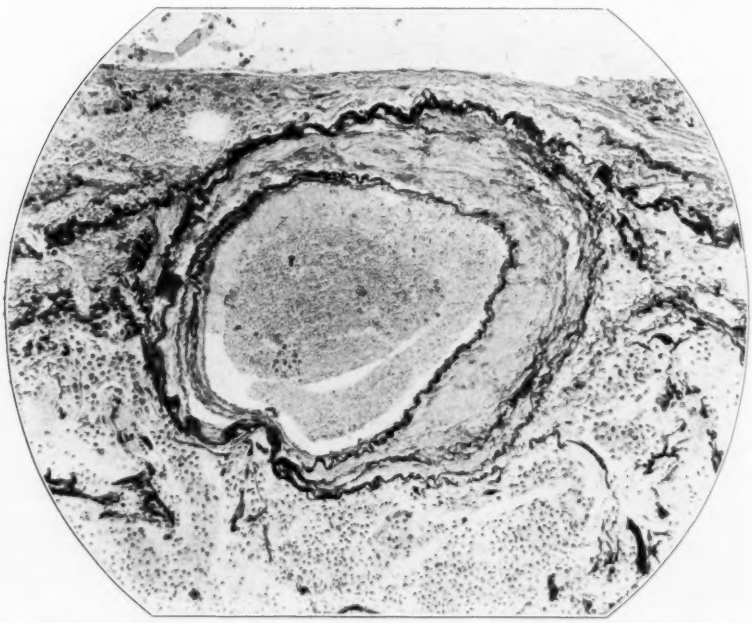

Fig. 28.—Photomicrograph of a transverse section of a small muscular artery (× 130; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). There is fibrosis of the media affecting the upper and right sides of the vessel.

into the thickened intima through the media from the adventitia (fig. 29). 2. A man with an aortic aneurysm compressing the left bronchus and with bronchiectasis of the left lung. In some of the small muscular arteries of the left lung the media in parts was replaced by vascular and cellular fibrous tissue. 3 and 4. Two cases of pulmonary tuberculosis. The media of some small arteries near tuberculous foci showed dense fibrosis of the media with round cell infiltration.

Fibrosis was present in 4 of 30 patients under 40 (13 per cent) and in 29 of 70 over 40 (42 per cent). Three of the 4 patients under

40 had rheumatic cardiac disease with congestive heart failure. In these the fibrosis may have been due either to healed rheumatic arteritis or possibly to the increased wear and tear due to the increased pulmonary vascular pressure. Of the patients over 40, 27 per cent in the "no cause" group and 90 per cent in the "pulmonary and cardiac disease" group showed fibrosis (table 31). Thus, fibrosis of the media, except in cases of inflammatory origin, is chiefly seen in elderly persons, but the presence of cardiac or pulmonary disease alone and especially together, increases

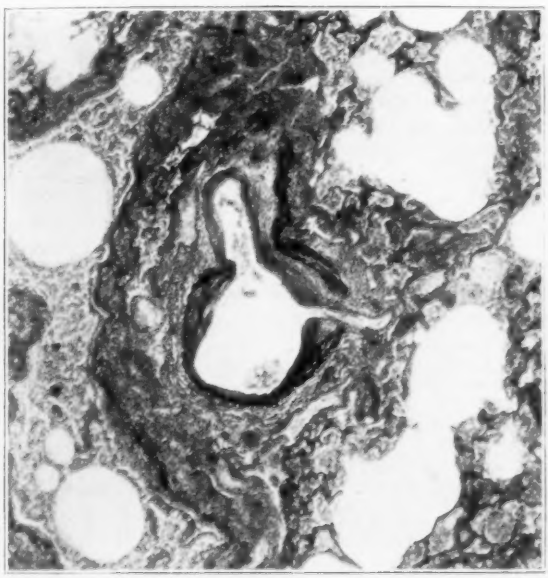

Fig. 29.—Photomicrograph of a section of a muscular artery (× 28; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). There is thick cellular adventitia. In several places the elastic tissue and muscle of the media have been destroyed (to the right at the origin of the branch, above and to the left) and cellular vascular connective tissue is continuous from the adventitia, through the destroyed media to the thickened intima.

the incidence, perhaps because of an associated rise in the pulmonary vascular pressure.

SYPHILIS OF THE PULMONARY ARTERIES

There has been an undue tendency, especially on the part of French and South American authors to exaggerate the frequency of syphilis of the pulmonary vessels and the importance of syphilis in the pathology of the vessels of the pulmonary circulation. Many cases have been

called syphilitic in the absence of satisfactory evidence and even in the presence of a satisfactory alternative cause. One case of syphilis of the pulmonary artery was found in the 100 cases in the present series. This will be described before passing on to a discussion of the condition.

REPORT OF CASE 3

History and Course.—G. T. L., a man, aged 43 at his death, gave a history of gonorrhea at the age of 17 and of syphilis at 19. Nine years before admission he began to have low substernal distress, especially when the stomach was empty. Two years later he had two severe hematemeses, followed by edema of the legs, ascites and dyspnea on exertion. The abdomen was tapped, and 9½ pints (4,500 cc.) of fluid was withdrawn. The liver was enlarged. The heart was large, and there were aortic systolic and diastolic murmurs. The blood pressure was 160 systolic and 110 diastolic. The Wassermann reaction was positive. The patient was markedly anemic.

TABLE 31.—*Distribution of Fibrosis of the Media According to Age and Etiologic Factor*

	Patients Less Than 40 Years of Age		Patients Over 40 Years of Age		
				Patients with Fibrosis	
Etiologic Factor	Number of Patients	Patients with Fibrosis	Number of Patients	Number	Percentage
No cause	16	0	15	4	27
Pulmonary disease	6	0	23	11	48
Cardiac disease	2	2	5	2	40
Hypertension	3	1	6	1	17
Pulmonary and cardiac disease	3	1	10	9	90
Cardiac disease and hypertension	..	..	4	1	25
Pulmonary and cardiac disease and hypertension	..	..	3	0	..
Pulmonary disease and hypertension	..	..	5	3	60

After discharge ascites and edema persisted. Occasional attacks of nocturnal dyspnea began three years before admission to the hospital.

Examination showed that the patient was thin, the face was pale and the lips were brick red. The right side of the chest was fixed, and smaller than the left. There were many dilated veins across the upper part of the chest. The right side of the chest was dull on percussion, and faint bronchial breathing and many crepitations were noted. The base of the left lung was also dull. The left border of the cardiac dulness was 10 cm. from the midline, 2.5 cm. outside the midclavicular line. There were aortic systolic and faint diastolic murmurs. The peripheral vessels were thickened. Pulsus alternans was present. The abdomen was enormously swollen by ascites, and the skin was red and hot; the legs and thighs also were edematous and reddened.

The blood count showed 4,180,000 erythrocytes and 70 per cent of hemoglobin. The Wassermann reaction was positive. The electrocardiogram showed left bundle branch block and a low voltage.

Omentopexy was performed, and the patient died rather suddenly on the next day.

Gross Postmortem Observation.—Autopsy showed the body of a fairly well developed middle-aged man with great edema of the legs and scrotum and a

recent abdominal operative wound. The peritoneal surface was smooth and glistening. The right pleura was densely adherent to the lung except on its lower surface, where it was greatly thickened and formed a sac enclosing 1,300 cc. of serous fluid. The left pleura contained 900 cc. of fluid. The anterior portion of the lower border of the left upper lobe was bent on itself and adherent in its new position to the portion of lung above and behind it. The right lung was compressed to less than half its normal size. The vessels and bronchi stood out prominently on the cut surface. The left lung was edematous and showed emphysema of the anterior border.

The pericardium contained 50 cc. of serous fluid and was densely adherent over the right auricle. There were more recent adhesions over the pulmonary artery and the base of the left ventricle.

The heart was moderately enlarged. The right ventricle was hypertrophied (from 5 to 9 mm. thick). The left ventricle was dilated and slightly hypertrophied (18 mm. thick at the base and 8 mm. near the apex). Near the apex the portion of the myocardium nearest the endocardium was scarred, and there was another scar at the base of the left ventricle. The aortic cusps showed a slender row of glistening granules at the lines of closure. The pulmonary cusps were slightly enlarged, and there was a small pinkish nodule in the center of each. The mitral and tricuspid rings were slightly dilated. The orifice of the right coronary artery was greatly, and that of the left slightly, narrowed. The left coronary artery showed a great deal of arteriosclerosis with calcification and narrowing of the lumen. The thoracic aorta showed marked atheroma and syphilitic aortitis, together with a tendency to bulging. The pulmonary arteries were dilated (circumference 8.4 cm. at the valve, 9.4 cm. 2 cm. above the valve and 8.7 cm. at the right hilus and 5.4 cm. at the left). The intima of the stem appeared normal. There were a few slightly raised whitish-yellow patches in the main right and left arteries, and in the main intrapulmonary branches they were more prominent. The branch to the middle lobe of the right lung was blocked at its mouth by a firm, adherent, reddish-gray thrombus. Just proximal to this there was an area about 1 cm. square of thickening and longitudinal wrinkling of the intima. The pulmonary veins appeared normal. The venae cavae and the portal, hepatic, splenic and superior mesenteric veins appeared normal.

The liver was normal in size. It was coarsely nodular and showed patchy capsular thickening. The spleen was large and firm, with patchy capsular thickening. The kidneys were small, the capsule was slightly adherent, the surface was coarsely granular with irregular scars and the markings were obscured.

Microscopic Postmortem Examination.—The pulmonary arterial stem showed slight patchy intimal thickening to a maximum of 0.07 mm. of the usual type. The media was greatly thickened (1.83 mm.). In the superficial part of the media were fairly large areas, in which muscle was absent, containing loose fibrillar connective tissue and elastic membranes together with some blood vessels, around some of which there was a scanty lymphocytic infiltration. The elastic tissue was not interrupted by this, only pushed aside. The adventitia showed a little diffuse lymphocytic infiltration. Many of the vasa vasorum showed a thick layer of longitudinal muscle outside an inner circular muscle layer, and in some the inner circular layer was replaced by dense fibrous tissue. The intima of the right main pulmonary artery was enormously thickened (from 0.42 to 1.59 mm.) with sudden diminutions and increases in the thickness, giving the impression of a series of parallel furrows in the intima. It consisted of dense connective tissue with a few round and spindle cells. Near the surface and parallel to it was a thin broken streak of calcification. In the depths of the intima were irregular clefts

left by the solution of cholesterol deposits. The media in most of its extent showed a normal structure, but in one long stretch its whole thickness was replaced by dense, rather vascular connective tissue with a few lymphocytes (fig. 30). The muscle and elastic laminae, except for a few fragments, were completely destroyed. There was slight diffuse lymphocytic infiltration in the adventitia, somewhat more marked around the vasa vasorum.

The branch to the right middle lobe contained a large unorganized, laminated thrombus of fused platelets and fibrin with very few red blood cells. The intima showed changes similar to those in the right main artery, but the media and adventitia were normal.

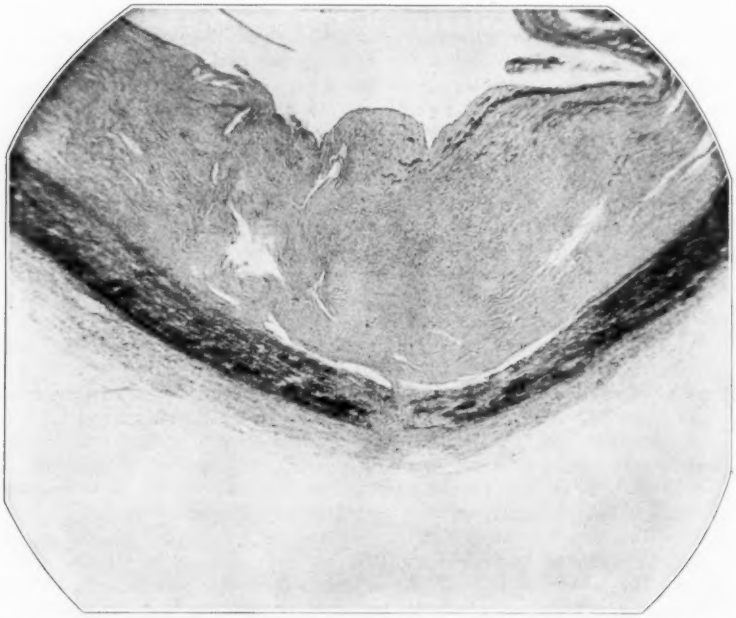

Fig. 30.—Photomicrograph of a section of a right main pulmonary artery (× 60; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). There is great intimal thickening, with numbers of fat spaces, and near the surface, to the right, a streak of calcification. The media near the center shows destruction of the elastic laminae and muscle and replacement by dense vasculocellular fibrous tissue. There is diffuse lymphocytic infiltration in the adventitia.

The elastic intrapulmonary branches (over 1 mm. in diameter) all showed patchy or diffuse intimal thickening, sometimes relatively enormous (e. g., 0.63 mm. in an artery 1.56 mm. in external diameter), often with great narrowing of the lumen. The intima consisted of connective tissue with numbers of lymphocytes, fibroblasts and irregular muscle cells and a great deal of elastic tissue in the depths. The media was normal. The adventitia often showed engorged capillaries and venules, and many of the vasa vasorum show narrowing of the lumen

by great intimal thickening either by dense connective tissue or by closely packed oval or polygonal cells, similar to the second type of endarteritis obliterans, previously described.

One artery, 2.66 mm. in diameter, showed opposite the origin of a partly occluded large branch a conical horn-shaped mass projecting for 1.36 mm. into the lumen. It consisted of dense connective tissue with many elastic fibers, smooth muscle cells, lymphocytes and large mononuclears. There were also numbers of vascular lumens. The horn appeared to be due to the organization of a thrombus of the branch projecting into the parent vessel. This branch was a muscular artery, 0.96 mm. in diameter, the lumen of which was blocked for the first 1.5 mm. of its course by dense connective tissue containing elastic fibers, muscle cells and numbers of endothelium-lined lumens. Several other small muscular arteries showed similar changes, probably also due to the organization of thrombi. Others showed what appeared to be organized parietal thrombi, with many capillary lumens in the thickened intima. All the remaining small muscular arteries showed slight or great patchy or diffuse intimal thickening, often with great narrowing of the lumen. The thickened intima consisted of dense connective tissue, with round and spindle cells and often some irregular elastic tissue. The media in most of the arteries was normal, but in some (fig. 29) the muscle and internal and external elastic laminae were destroyed by the ingrowth from the adventitia into the thickened intima of dense or loose connective tissue, with lymphocytes, large mononuclears, capillary lumens and sometimes granules of coal pigment. This change occurred in some but not all the arteries with organized thrombi and in some others in which the intimal thickening was not obviously due to the organization of a thrombus. In these arteries the adventitia was thick and dense and showed diffuse infiltration with lymphocytes, plasma cells, large mononuclears and coal pigment.

The arterioles and venules showed thickened walls, often with a few lymphocytes and large mononuclears. The small veins showed a similar structure.

The larger veins showed intimal thickening, sometimes with narrowing of the lumen, consisting of dense connective tissue with a few lymphocytes, large mononuclears and muscle cells. The media appeared normal except for a scanty lymphocytic infiltration in a few veins. The adventitia was thick and dense and showed a little diffuse lymphocytic infiltration.

The lung tissue showed a great deal of collapse, especially in the right lung, and thickening of most of the alveolar walls, with fibrosis and infiltration with lymphocytes and large mononuclears. The bronchi were dilated, and their epithelium was proliferated and desquamated, almost filling the lumen, together with lymphocytes and large mononuclears in some cases. The walls were swollen and infiltrated with lymphocytes, large mononuclears and a few plasma cells.

The aorta showed syphilitic aortitis with a great deal of scarring of the media.

The descending branch of the left coronary artery was occluded by an organized thrombus.

Some of the arteries of the pancreas, kidney, spleen and adrenal glands showed connective tissue thickening of the intima and hyperplasia of the elastic tissue.

Comment.—The changes in the right pulmonary artery seemed to be undoubtedly syphilitic. They were similar to those in the aorta, which were characteristic of syphilitic aortitis. This, together with the positive Wassermann reaction, appeared to be conclusive evidence.

The changes in the small muscular arteries were more difficult to interpret. The changes in the intima (except those due to the organization of thrombi) were those of ordinary severe arteriosclerosis. The destruction of the media of some of the vessels and replacement by vascular cellular fibrous tissue might have been due to the following causes: 1. The growth of vascular connective tissue from the adventitia through the media into the intima may have been connected with the organization of thrombi, the vessels representing the organizing capillaries. This is unlikely because the change occurred in some vessels with no evidence of organizing thrombi and because in other cases the organization of thrombi was not associated with destruction of the underlying media by the ingrowth of vascular connective tissue from the adventitia. 2. The change may have been only the common senile fibrosis of the media, but in this condition the whole thickness of the media is rarely involved, and the fibrous tissue is dense, avascular and acellular. 3. The process may have been syphilitic. The lesions were similar to those in the aorta and right pulmonary artery, allowance being made for the different structure of the vessels. In systemic vessels of this size the common syphilitic lesion is endarteritis obliterans, though gummatous invasion followed by fibrosis may occur. It is therefore probable, though not absolutely certain, that the changes in the small arteries also were syphilitic. The other changes were nonspecific.

The clinical features of the case were atypical. It was recognized that there was something unusual, but syphilis of the pulmonary vessels was not thought of, and even in the light of the postmortem observations it is difficult to see how the diagnosis could have been made. Indeed, it seems likely that the pulmonary vascular changes played comparatively little part in causing the symptoms.

COMMENT

There is an extensive literature on syphilis of the pulmonary arteries. Records of 65 patients thought to be syphilitic have been found in the literature, but in only 14 of these [x] could the diagnosis be taken as being reasonably well established. In the others autopsy was not performed or the postmortem observations were doubtful or definitely did not confirm the diagnosis of syphilis. In some cases rheumatic cardiac disease was present, and the changes in the pulmonary artery were most probably those of rheumatism and not of syphilis.[y]

Of the 15 patients (including the 1 patient whose case is here reported), 7 were men, and 8, women. The age ranged from 28 to 60

(*x*) 25, 57, 141, 154, 170, 231, 236 (2 cases), 238, 247, 311 (3 cases), 313.
(*y*) 53, 298, 317.

(average, 45). Thus, as far as can be judged from the scanty statistics available, syphilis of the pulmonary artery occurs rather earlier than that of the aorta, and there is not the same great preponderance of cases in men.

MORBID ANATOMY

Usually only the large vessels are involved, though in case 3 reported here and in Plenge's first case the small vessels showed changes which were possibly syphilitic, and in Peck's case they showed endarteritis obliterans. In the other cases in which the small vessels were examined, only nonspecific changes were observed. In none of the cases in which the diagnosis was reasonably well established were the changes confined to the small vessels though this was so in some of the cases in which the diagnosis was doubtful or obviously wrong.

It is rarely possible to make the diagnosis macroscopically, though in case 3 reported here and in some others [z] there were suggestive scarring (linear, radiating or depressed) and localized bulging. In 7 cases aneurysms were present.[a] In 3 of these [b] the aneurysm involved the stem of the pulmonary artery and was fusiform. In another [25] there was a saccular aneurysm of the stem. In 1 [170] there was a saccular aneurysm of the right pulmonary artery; in another, an aneurysm of the left pulmonary artery (Warthin,[311] case 3), and in the last the exact site was not stated (Warthin, case 1). The saccular aneurysm usually contained a laminated thrombus. In Plenge's case 1 there was a dissecting aneurysm which had ruptured into the pericardium. Occasionally, recognizable gummas were present in the myocardium [154] or between the roots of the aorta and the pulmonary artery.[313]

The stem and main branches of the pulmonary artery were usually dilated, but in Barth's case there was marked narrowing of the left pulmonary artery by a ring of fibrous tissue.

Secondary atherosclerotic changes in large and small arteries were common. Thrombi were present in the cases in which there were saccular aneurysms. In Ploeger's case the thrombus involved also the stem of the pulmonary artery, greatly narrowing it. Thrombi were also present in the cases of Karsner and Peck.

The heart was always slightly or greatly enlarged, its weight being from 430 to 750 Gm. In the cases of Ploeger, Plenge (case 1) and Warthin (case 2) only the right ventricle was hypertrophied; in the others both ventricles were involved. In Kux' case the cusps of the pulmonary valve were scarred and shrunken, and the tricuspid valve showed evidences of gummatous endocarditis. Syphilitic aortitis was

(*z*) 25, 236, 238, 313.
(*a*) 25, 170, 236, 238, 247, 311 (2 cases).
(*b*) 236, 238, 247.

present in all cases except those of Plenge (case 1), Peck and Letulle. Myocardial changes were present in some cases. In case 3 reported here there was the scar of an old infarct in the left ventricle. In Letulle's case there was a localized aneurysmal bulge of the right auricle. In Kux' case there were multiple myocardial gummas, and similar changes were present (though the diagnosis was not confirmed microscopically) in Handford's case.[124]

The lungs often showed evidences of emphysema, fibrosis, bronchiectasis and old tuberculosis. Pleural adhesions were common. The other organs usually showed chronic venous congestion.

MICROSCOPIC CHANGES

Microscopic changes were commonest in the stem of the pulmonary artery and its main branches, where the appearances were those of syphilitic mesarteritis and periarteritis. The intima usually showed slight or severe atherosclerosis, the greatest thickness in any case[238] being 0.5 mm. It consisted of dense hyaline fibrous tissue, often with fat either lying free or in large foam cells. In Ploeger's case there was a deposit of lime near the surface. In his case, too, a partly organized thrombus was present, and there were capillaries in the depths of the intima even in areas not covered by the thrombus. In some cases[c] the intima showed gummatous changes together with areas of necrosis and infiltration with lymphocytes and plasma cells. The media showed larger or smaller patches of fibrosis breaking up and destroying the elastic laminae. Often there was an ingrowth of vessels, frequently showing endarteritis obliterans, surrounded by an infiltration of lymphocytes, plasma cells, fibroblasts and occasionally[313] large multinuclear giant cells. In several cases[d] gummas were present. The adventitia showed foci of infiltration with lymphocytes and often plasma cells, usually most marked around the vasa vasorum, which often showed endarteritis obliterans, sometimes so advanced as to occlude them completely.

The changes in the right and the left pulmonary artery ascribed to syphilis were similar to those in the stem. In Karsner's case the left artery was obliterated by dense fibrous tissue, apparently representing an organized thrombus.

Syphilitic changes have been described in the large intrapulmonary arteries in several cases, but in none of these was the diagnosis free from doubt, and usually it was clearly erroneous. The changes were usually those of simple atherosclerosis, though sometimes there was scanty round cell infiltration of the adventitia and media.

(*c*) 154, 231, 236 (case 2), 313.

(*d*) 57, 154, 311 (cases 1 and 2), 313.

In the small muscular arteries the changes were usually those of simple atherosclerosis, sometimes with thrombosis and organization. The case in which the lesions most clearly resembled those of syphilis was case 3 described here, in which many of the small arteries showed destruction of the muscle and elastic tissue of the media by cellular connective tissue.

Spirochetes were found only in Warthin's case. Arrillaga [12] reported the presence of spirochetes in the peribronchial and lymphoid tissue in one of his cases in which the lesion was almost certainly not syphilitic. The spirochete in this case was probably a saprophytic organism inhabiting infected bronchi, and not Spirochaeta pallida.

The lungs frequently showed emphysema, fibrosis and bronchiectasis, and those lesions probably were important in the production of the symptoms.

Syphilis of the pulmonary arteries is thus essentially a disease of the larger vessels, in spite of all that has been written on the importance of syphilitic pulmonary endarteritis obliterans in the production of symptoms (see the section on Ayerza's disease).

SYMPTOMS

The onset was usually insidious, with increasing dyspnea on exertion, but occasionally, as in Warthin's third case, in which the first symptom was profuse hemoptysis, it was sudden. In other cases the first symptom, often preceding others by years, was cough with expectoration and sometimes attacks of asthma. Dyspnea of some degree was absent only in Barth's case, in which there were no cardiac symptoms. Usually it was severe, with orthopnea, but in Letulle's case it was inconspicuous compared with the other symptoms. Cyanosis was common, being sometimes [170] the most striking sign. In others [e] (including case 3 described here) it was absent. Edema was sometimes absent and usually was slight and appeared late, but in case 3 there were marked ascites, pleural effusion and edema of the legs. Blood streaking of the sputum or slight hemoptysis was common. In Warthin's case 3 there was severe and repeated hemoptysis that was not explained at autopsy. Retrosternal pain on exertion occurred in 3 cases [f] (including case 3 described here), in all of which syphilitic aortitis was also present. Nervous symptoms were sometimes present. In the late stages of the disease some patients had troublesome insomnia, while others became increasingly drowsy and stuporous. Barth's patient had a stroke followed by progressive dementia twelve months before death. Attacks

(*e*) 25, 311, 313.

(*f*) 238, 313.

of Adams-Stokes' disease were present in 2 cases [g] in which there were gummas of the myocardium.

Examination often showed changes in the heart and lungs. In Ploeger's case of aneurysm of the pulmonary artery there was a localized bulge of the upper part of the precordia. The heart was usually slightly enlarged to the left. Enlargement to the right was rarely detected, perhaps owing to the frequent presence of emphysema. The pulmonary second sound was often accentuated. Pulmonary systolic murmurs were common, and a pulmonary diastolic murmur was heard in 3 cases (Clarke's and both of Plenge's), though it was difficult to distinguish it from the murmur of syphilitic aortic incompetence. Pericardial friction developed toward the end in Warthin's third case.

Signs of congestion and edema of the bases of the lungs and of chronic bronchitis and emphysema were common. In 2 cases [h] there was evidence of local pulmonary fibrosis. Clubbing of the fingers was present in 1 case.[238]

The liver was usually enlarged and in 1 case [238] the spleen also. Roentgenograms usually showed cardiac enlargement, particularly of the right side with a globular cardiac shadow. There was prominence of the left middle arc and in Ploeger's case evidence of enormous dilatation of the pulmonary artery, with no evidence of dilatation of the left auricle. The aorta also was often dilated.

The electrocardiogram in Kux' case showed complete heart block and right axis deviation; in Karsner's case, only an inverted T wave in lead III, and in the case reported previously, left bundle branch block and a low voltage.

The Wassermann reaction either was negative or was not mentioned in 7 cases,[i] in all of which the histologic lesions were characteristic of syphilis.

The course of the disease was almost always steadily downhill from the moment cardiac symptoms appeared though in a few cases there was transient improvement while the patient was in the hospital. The duration of symptoms in the cases in which it was recorded was from six weeks to forty years (average, eight years). In the cases in which there was a long history the symptoms for many years were merely those of chronic bronchitis, and it does not seem legitimate to attribute those symptoms to syphilis of the pulmonary arteries, though some authors have done so. Symptoms of heart failure usually did not last for more than a few months, though occasionally mild heart failure lasted for years. The usual mode of death was progressive congestive

(*g*) 124, 154.
(*h*) 25, 238.
(*i*) 25, 170, 231, 236, 238, 311, 313.

heart failure, with increasing dyspnea, cyanosis and edema. In some cases death was sudden, owing to thrombosis of a large pulmonary artery [170] or to rupture of a dissecting aneurysm of the pulmonary artery into the pericardium,[236] in an attack of Adams-Stokes' disease [154] or in an attack of angina.[313]

DIAGNOSIS

Diagnosis is difficult and often impossible in the present state of knowledge. Syphilis of the pulmonary arteries may be suspected if in a syphilitic patient there is heart failure with or without marked cyanosis and with evidence of hypertrophy of the right ventricle on physical examination (enlargement of the heart to the right, forcible right ventricular pulsation in the epigastrium, accentuated pulmonary second sound), by roentgenograms (enlargement of the right ventricle, prominence of the conus of the right ventricle and of the pulmonary artery) and by electrocardiogram (preponderance of the right ventricle). Roentgenographic evidence of an aneurysm of the pulmonary artery, in the absence of congenital cardiac disease, is also important. In most of the cases that have been reported these requirements were not fulfilled.

TREATMENT

Treatment in the stage of congestive heart failure is hopeless. Probably efficient treatment of early syphilis would prevent the occurrence of heart failure. If a diagnosis could be made before heart failure occurs, perhaps antisyphilitic treatment could hold the condition in check for years. When congestive heart failure is present, only symptomatic treatment with rest, digitalis and diuretics is possible. This can only delay, not prevent, the fatal issue.

AYERZA'S DISEASE

The concept of Ayerza's disease has dominated the American, English and French literature for thirty years. The meaning of the term is not fixed. To some it means any condition of cardiac failure associated with disease of the pulmonary vessels. Others identify it, unjustifiably, with primary pulmonary vascular sclerosis. Ayerza, of Buenos Aires, in 1901 described in an unpublished clinical lecture a case of heart failure with such marked cyanosis that the patient was almost black (*cardiaco negro*). At autopsy there were dilatation of the bronchi, peribronchitis, and hypertrophy and dilatation of the right auricle and ventricle. The pulmonary vessels were not mentioned. In 1905 Escudero found at autopsy in a similar case evidence of atherosclerosis of the stem and main extrapulmonary and intrapulmonary branches of the pulmonary artery. Marty in 1909 first called the condition Ayerza's disease. In 1912 Arrillaga concluded that the arterial

lesions were secondary to chronic bronchopulmonary disease. In 1913 he [8] stated that the chief cause of the symptoms was chronic respiratory disease with emphysema and that chronic infections, such as syphilis and malaria, and chronic alcoholism sensitize the vascular sytsem so that mechanical changes in the pulmonary circulation, which usually produce only slight changes in the pulmonary vessels, cause marked lesions. In 1916 he described a case in which there was an aneurysm of the pulmonary artery. In 1917 Barlaro [22] said that the condition might be due to many causes, of which syphilis was the commonest. In 1917 Warthin [311] described a case of syphilis of the pulmonary artery in which Spirochaeta pallida was demonstrated in the lesions. This patient was pale and showed none of the symptoms of Ayerza's disease, but since then the Argentinian authors have been strongly biased in favor of a syphilitic origin of Ayerza's disease. In 1921 Arrillaga [12] described a case with pulmonary lesions which were termed syphilitic bronchitis and bronchopneumonia in which he found a spirochete which he assumed to be Spirochaeta pallida in the bronchial lesions and in the adventitia of the arteries. The description was inadequate, and it seems probable that it was really a nonspecific spirochete of the kind so often found in the mouth and in infected bronchi. By 1924 Arrillaga [9] had come to the conclusion that the essential factor is syphilis of the pulmonary arteries, and that chronic pulmonary disease, mitral stenosis and other conditions are important only in that by putting a strain on the pulmonary arteries they favor the localization of the syphilitic process there. But the evidence of the syphilitic nature of the pulmonary arterial disease in Arrillaga's cases is more than doubtful, and some Argentinian authors, for instance, Brachetto-Brian,[46] have stated that the lesions in each of their cases was merely atherosclerosis. In 1926 Escudero,[100] another of Ayerza's pupils, said that all patients with chronic pulmonary disease who die of failure of the right heart are deeply cyanosed and are therefore *cardiaques noirs,* but that in the absence of the lesions that he believed characteristic they do not have Ayerza's disease; conversely, patients with Ayerza's disease in the early stages are not cyanosed, and therefore are not *cardiaques noirs.* The lesions that he believed to be necessary for the diagnosis of Ayerza's disease are bronchial syphilis and obliterating sclerosis of the pulmonary vessels, which need not be syphilitic. Brachetto-Brian [40] expressed the belief that there are no specific lesions of Ayerza's disease. There is chronic disease of the bronchi and lungs, which may be, but usually is not, syphilitic; there is disease of the pulmonary vessels, usually atherosclerotic, but occasionally syphilitic, and there is hypertrophy with ultimate failure of the right heart. Syphilis, he said, is often present even when the lesions in the lungs and arteries are not syphilitic, so that a syphilitic soil favors the development of the disease. He regarded

the pulmonary lesions as primary, the vascular lesions being of the nature of a hypertrophic process followed by degeneration. The pulmonary arterial lesions in themselves he considered to be of little importance.

It is thus clear that there is no general agreement as to what constitutes Ayerza's disease. The consideration of some of the cases which have been described, now to be undertaken, raises the question as to whether the retention of the name is justified. Reports of 20 cases have been collected from the literature. Fifteen of the patients were men, and 5, women. The ages ranged from 28 to 62 years (average, 53).

MACROSCOPIC CHANGES

The heart was always enlarged, and the right auricle and ventricle were hypertrophied and dilated, the thickness of the ventricle ranging from 5 to 20 mm. The left auricle and ventricle were occasionally atrophic,[j] but more usually they were hypertrophied, though not so much as the right. In several there was marked sclerosis of the coronary artery. In 1 case [334] the cusps of the pulmonary valves were slightly thickened, but competent; in another [53] there was mitral stenosis, though the atheroma of the pulmonary arteries was ascribed, without a vestige of evidence, to syphilis. The aorta was occasionally narrow and hypoplastic.[k] Sometimes it showed syphilitic aortitis.[l]

The stem and main extrapulmonary and intrapulmonary branches of the pulmonary arteries were occasionally normal,[53] but usually there was atherosclerosis, most marked in the large intrapulmonary branches, diminishing in the extrapulmonary branches and often absent in the stem. In the smaller branches the patches at times somewhat narrowed the lumen, but the larger branches were, if anything, dilated. The smaller branches often were thick-walled and gaped widely on the cut surface of the lung. Thrombi were sometimes present[m] in small or large branches. In Ploeger's case [238] syphilis of the pulmonary artery with aneurysmal dilatation was present. In 3 of Arrillaga's cases [10] "aneurysmal" dilatation was present, and in 1 case the aneurysm had burst into the pericardium, but in none was there convincing evidence of syphilis.

Dense local or general pleural adhesions, chronic bronchitis with moderate tubular dilatation of the small and medium-sized bronchi, sometimes localized saccular bronchiectasis,[n] marked emphysema and

(*j*) 150, 238.
(*k*) 47, 150.
(*l*) 47, 54, 238, 334.
(*m*) 9, 40, 54, 238.
(*n*) 12, 40, 47, 238.

peribronchial and perivascular fibrosis, or occasionally atelectatic fibrosis of one or more lobes,[o] were present in practically all cases. In some cases [48] there were partially healed gummas destroying small bronchi and blood vessels. In all cases the lungs were congested and edematous, but infarcts were unusual even in the cases of arterial thrombosis.

MICROSCOPIC CHANGES

Microscopically the stem of the pulmonary artery sometimes showed more or less marked atherosclerosis,[p] and in 1 case there was a partly organized thrombus.[238] The media was usually normal but in 1 case it showed syphilitic mesarteritis,[238] in 1 a broad band of dense fibrous tissue [47] and in 1 slight round cell infiltration,[334] changes that were possibly syphilitic. The adventitia occasionally [q] showed round cell infiltration, chiefly perivascular and sometimes consisting predominantly of plasma cells. In the large extrapulmonary and intrapulmonary pulmonary arteries atherosclerosis was usually present, and thrombi, often organized, were seen. The media was usually normal apart from minor changes in the amount of elastic tissue though occasionally it was sclerosed [167] and in 1 case [334] there was a little round cell infiltration. The adventitia occasionally was thickened and sometimes showed slight round cell infiltration.

The small arteries were often narrowed, though sometimes they were dilated.[r] The intima was thickened in many, sometimes to the point of obliteration, by dense fibrous tissue or sometimes by organized thrombi.[40] The media was normal except in 1 case,[334] in which it showed slight round cell infiltration. The adventitia occasionally showed foci of lymphocytes and plasma cells,[s] described as miliary gummas.

SYMPTOMS

The onset was usually insidious. It was often preceded for many years by chronic cough with expectoration, but sometimes the earliest symptoms were those of gradually increasing congestive heart failure. Escudero [100] divided the course of the disease into three stages: 1. A prolonged bronchitic stage differentiated from ordinary chronic bronchitis only by the presence of polycythemia. The physical signs of chronic bronchitis and emphysema and sometimes of localized fibrosis of the lungs [t] are present. Sometimes this stage is absent, though often,

(*o*) 47, 238.
(*p*) 40, 47, 150, 334.
(*q*) 47, 238, 334.
(*r*) 12, 334.
(*s*) 2, 12.
(*t*) 47, 331.

even when the first symptoms are those of heart failure, the physical signs of chronic bronchopulmonary disease are present. 2. A stage of compensated cardiac disease, in which in addition to the foregoing, the physical signs of enlargement of the right heart are present. It is unusual for the patient to come under observation at this stage, and the signs of enlargement of the right heart are notoriously difficult to detect. 3. The stage of heart failure, with increasing dyspnea on exertion, which, however, is often slight compared with the other symptoms, great edema with ascites (this also is sometimes not marked) and deep cyanosis, often associated with headache, mental confusion and somnolence. In the cases reported the heart was usually slightly or moderately enlarged, especially to the right. Its rhythm was rapid and regular (in 1 exceptional case [54] there was auricular fibrillation). Gallop rhythm, best heard over the right ventricle, was sometimes present.[u] There were often systolic murmurs at the mitral, tricuspid and pulmonary areas and occasionally [9] a diastolic murmur of relative pulmonary incompetence. The pulmonary second sound was often but not always accentuated.[54] The red blood cell count ranged from 5,280,000 to 8,500,000. The leukocyte count also was sometimes raised, the highest recorded being 20,500. The roentgenogram usually showed moderate enlargement of the heart to the right and dilatation of the pulmonary artery but not of the left auricle. The electrocardiogram, in the few cases in which it was recorded, showed preponderance of the right ventricle, sometimes with inversion of the T wave in leads II and III.[v] In 1 case [9] there was bundle branch block of the common type. The Wassermann reaction was positive in 11 cases, negative in 3 and not recorded in 6.

The course of the disease after heart failure has appeared was usually steadily progressive, but occasionally remissions lasting for a few weeks or months occurred.[w] Death usually was due to heart failure, though sometimes it was due to some intercurrent disease, especially bronchopneumonia. The duration of cardiac symptoms was usually from one to four years, but the bronchitic symptoms may have been present for many years before heart failure occurred.

COMMENT

It is clear that there is nothing specific about the symptoms, which are those ordinarily recognized to be due to heart failure secondary to chronic bronchopulmonary disease. In such cases hypertrophy of the right ventricle is known to occur, though probably it is not so common as

(*u*) 2, 9, 167.
(*v*) 47, 150.
(*w*) 16, 47, 238.

is usually believed. Independent cardiac disease is usually present, in addition to the chronic pulmonary disease, and it is noteworthy that in the cases of Ayerza's disease that have been recorded the left as well as the right ventricle was often found to be hypertrophied, and coronary arterial disease and syphilitic aortitis were also commonly present at autopsy. Cyanosis is always marked when heart failure is complicated by severe chronic bronchopulmonary disease, and polycythemia usually accompanies chronic cyanosis of whatever cause. The lesions in the pulmonary arteries almost always seem to be those of atherosclerosis of a degree less marked than that in some cases in which there are no cardiovascular symptoms. True syphilis of the pulmonary arteries rarely occurs with this syndrome, and it sometimes occurs without the symptom complex of Ayerza's disease. Syphilis was proved to be present in only half of the cases that have been reported, and in only 1 of these was there acceptable evidence that the pulmonary arterial lesions were due to syphilis.

There is thus no clearcut, universally acceptable definition of Ayerza's disease, the term having a different significance to almost every writer on the subject; the lesions in the cases that have been reported were merely those of chronic pulmonary disease with moderate atherosclerosis of the pulmonary vessels and hypertrophy of the right ventricle; and the symptoms were merely those of heart failure associated with chronic disease of the lung. There seems to be no good reason for retaining the term Ayerza's disease.

(*To be concluded*)

Progress in Internal Medicine

SYPHILIS

A REVIEW OF THE RECENT LITERATURE

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The following review covers the literature on syphilis for 1934 and the first six months of 1935. A few of the more important papers appearing in 1933 have also been cited, particularly when necessary for the sake of continuity. In view of the large number of titles involved (the "Quarterly Cumulative Index Medicus" for 1934 lists 932 titles under the heading syphilis alone, not including those listed under drugs, organs, Spirochaeta pallida and diseases such as aortitis, neurosyphilis, dementia paralytica and tabes dorsalis), it has been necessary to exercise a rather rigid selection. Except for one important article with clinical applications, almost all reference to the serodiagnosis of syphilis has been omitted. In the field of experimental syphilis relatively few articles have been mentioned. In the more purely clinical field preference has been given to articles in the English and American literature, though I believe that the more important German and French literature also has been adequately covered. An attempt has been made to include also reference to articles which provide an adequate bibliography of the subject covered.

HISTORY OF SYPHILIS

Reawakened interest in the history of syphilis is apparent in a number of recent papers which do not lend themselves to review but which must be listed in a general summary of the subject. The more important of these articles are those by Holcomb,[1] Butler and Biello,[2] Moore and Solomon,[3] Zimmermann,[4] Klein [5] and Hendrickson.[6]

From the Syphilis Division of the Medical Clinic of the Johns Hopkins Hospital.

1. Holcomb, R. C.: Christopher Columbus and the American Origin of Syphilis, U. S. Nav. M. Bull. **32**:401, 1934.

2. Butler, C. S., and Biello, J. A.: The Influence of Ruy Diaz de Isla upon the Question of the American Origin of Syphilis, South. M. J. **26**:438, 1933.

3. Moore, M., and Solomon, H. C.: Contributions of Haslam, Bayle, and Esmarch and Jessen to the History of Neurosyphilis, Arch. Neurol. & Psychiat. **32**:804 (Oct.) 1934; Contributors to the History of Syphilis of the Nervous System: Ulrich von Hutten (1488-1524), Arch. Dermat. & Syph. **31**:692 (May) 1935.

(Footnotes continued on next page)

SPIROCHAETA PALLIDA

In an interesting article, which is particularly valuable to the English and American reader for its bibliography, Bessemans and his associates [7] discuss a wide variety of experimental facts bearing on the question of an invisible form of Spirochaeta pallida. The bibliography contains, in addition to references on this subject, a practically complete list of Bessemans' own work on many related topics, particularly in the field of experimental pyretotherapy.

The authors point out that the evidence for the existence of a life cycle of the spirochete, including some phase other than the spiral form, rests (1) on the demonstration, especially by silver staining methods and in tissues, of granules and of apparent transitional forms between these and the typical spiral forms; (2) on the seeming incongruity between the infectious potency of tissues (especially lymph nodes) from experimental animals and the extreme difficulty of demonstrating spirochetes in these organs, and (3) on the observations of Levaditi and his associates [8] that when implants of syphilitic tissue are made in rabbits, these grafts pass through a "prespirochete phase," or initial pause, during which no spiral form is present, and then suddenly, with no apparent transition, enter on a phase in which numerous typical spirochetes are present.

Bessemans and his group, however, believing with others that the available evidence does not justify conclusions as to the existence of a granular form of spirochete, have performed a series of experiments the results of which may be summarized as follows:

The incubation period of the chancre is somewhat lower in rabbits and guinea-pigs inoculated with syphilitic tissues (lymph nodes, spleen and brain) in which spirochetes can be demonstrated only with difficulty or not at all than when the inoculum is spirochete-rich testicular syphiloma. When these various tissues are progressively diluted, the infec-

4. Zimmermann, E. L.: The Pathology of Syphilis as Revealed by Autopsies Performed Between 1563 and 1761, Bull. Inst. Hist. Med. **3**:355, 1935.

5. Klein, J. E.: LeClerc's Account of the Origin of Chemotherapy and the Introduction of Syphilis into Europe, Arch. Dermat. & Syph. **31**:324 (March) 1935.

6. Hendrickson, G. L.: The "Syphilis" of Girolamo Fracastoro, with Some Observations on the Origin and History of the Word "Syphilis," Bull. Inst. Hist. Med. **2**:515, 1934; in Bull. Johns Hopkins Hosp., November 1934.

7. Bessemans, A.; van Haelst, J., and DeWilde, J.: An Experimental Study of the Problem of the Existence of an Invisible Form of the Syphilitic Virus, and of Spontaneous Spirochetosis in Rabbits, Am. J. Syph. & Neurol. **19**:161, 1935.

8. Levaditi, C.; Vaisman, A.; Schoen, R., and Mezzer, J. G.: Cycle evolutif du virus syphilitique; neurosyphilis; virulence du T. Pallidum, Ann. Inst. Pasteur **50**:222, 1933.

tiousness of transplants of tissue from a popliteal lymph gland is from ten to fifty times weaker than that of tissue from testicular syphilomas. Spirochetes can always be demonstrated by dark-field examination in organs (lymph nodes) in which they have heretofore been found with great difficulty or not at all provided an appropriate technic is employed. With an ingenious mathematical formula it is possible even to calculate the approximate number of spirochetes in any organ. Utilizing this count, the authors have demonstrated a direct relationship between the number of spirochetes in a graft and the promptness of appearance of lesions following its transplantation; and they express the belief that by progressive dilution of tissues they can produce infection as long as a single spirochete (from lymphatic tissue) remains and that infection fails when the spiral form of the spirochete has finally disappeared (through dilution). The virus in lymph nodes is apparently of much greater virulence than that in testicular syphilomas, since fewer spirochetes are needed to infect with the former than with the latter tissue and since their thermoresistance is greater in lymphoid tissue. On the basis of these facts the authors state that there is no necessity for assuming the existence of a granular or invisible form of the virus and that the only infectious agent of syphilis is the visible spirochete.

Nyka [9] presents the opposite point of view. Clinically, it has been for a long time remarked that the disappearance of spirochetes, whether spontaneous or accelerated by treatment, is not synonymous with cure. On the contrary, the gravest complications often occur when one can no longer find spirochetes in the body. Two hypotheses may explain these facts: Either these complications are produced by some virus other than that of the spirochete or spirochetes can exist in some other form than the classic one. Schaudinn himself expressed belief in the second hypothesis, and a serious basis for that hypothesis was found in the work of Jacquet and Sézary [10] and of Levaditi, Schoen and Sanchis-Bayarri. Both of these groups of workers demonstrated totally different forms from the classic spirochete, ranging by intermediate stages to argentaffin granules of small dimensions. Numerous workers have noted that certain organisms, particularly those in the lymph nodes of rabbits, were virulent for normal animals, although spirochetes could not be demonstrated. However, a number of investigators and finally van Haelst [11] have demonstrated spirochetes in small numbers in these glands. Similar observations have been made on the mouse. There is, however, a marked contrast between the very small number of demonstrable organisms in these organs and often their total absence and, on the other

9. Nyka, W.: Le virus syphilitique: ses variations morphologiques, sa multiplication, et son action pathogène, Ann. Inst. Pasteur **53**:243, 1934.

10. Jacquet and Sézary: Bull. et mém. Soc. méd. d. hôp. de Paris **24**:114, 1907

11. van Haelst: Compt, rend. Soc. de biol. **113**:1535, 1933.

hand, their great virulence. In order to explain this phenomenon, Levaditi and his collaborators undertook a series of experiments which led them to express their belief in the existence of granular forms of the spirochete. This theory, however, has not been entirely accepted. The suggestion that the unknown form of the spirochete may be an ultravirus implies filtrability. However, no one has yet been able to demonstrate this feature.

Nyka states that by a series of experiments he has demonstrated the following facts: 1. The organism of syphilis has two distinct morphologic aspects—the spirochete and a filamentous form, with all grades of transitional forms between these two. 2. The transmission of syphilis is by the spirochetal form, the rôle and existence of which are ephemeral. The spirochetal form disappears once the infection is established in the new host. 3. The filamentous form constitutes the usual form of syphilitic virus in the body, and to it is to be attributed the characteristic pathologic picture of syphilis. 4. The change of morphologic form does not involve any modification of the biologic properties of the parasite. 5. In the spirochetal form the parasite can penetrate into cells and multiply in their interior, either in the cytoplasm or in the nucleus. As soon as it penetrates the interior of a cell it loses its spiral form and becomes a filament. This transformation can also occur outside the cell. The author maintains that he has continually seen this occur under the dark-field microscope. He has studied in this way a suspension of syphiloma in Ringer's solution mixed with equal parts of a suspension of mouse spleen and chicken embryo juice. 6. In its filamentous form the parasite can multiply by transverse division, and the filaments resulting from this division can be transformed again into spirochetes. 7. The multiplication of the parasite in the interior of a cell is not compatible with the survival of the cell. 8. All cells of the body do not present the same degree of vulnerability to syphilitic virus. Hepatic cells and fibroblasts are least sensitive; lymphoid cells and those of the nervous system are highly sensitive. 9. In the filamentous form the syphilitic virus has not heretofore been seen because of its feeble staining properties.

In addition to the dark-field studies Nyka has studied by silver impregnation methods tissue from infected rabbits, particularly lymph nodes, testicular syphilomas, spleen and liver, and from infected mice, particularly lymph nodes, liver and brain. To me his illustrations do not seem to be particularly convincing since he himself states that they do not lend themselves well to demonstration to others because of the precipitation of silver granules in many albuminous materials. He does not seem to have controlled his study by the examination of tissue from normal animals.

Gastinel and Pulvenis [12] have also studied one phase of the subject with the method used by Bessemans: the inoculation of rabbits with constantly increasing dilutions of syphilitic virus. As the concentration decreases the period of incubation lengthens, though the character of the lesion remains unchanged. When the amount of testicular emulsion was decreased below 0.001 cc., however, symptomless infection occurred (with amounts as small as 0.0005 cc.).

Morgan and Thomas [13] attempted to determine the minimum infective dose of spirochetes by using the Barbour single cell technic. While the method employed is not above criticism, they were unable to obtain successful inoculations of rabbits, symptomless or otherwise, by means of the intratesticular inoculation of from one to six spirochetes.

Culture of S. Pallida.—As a result of personal experiments and of a thorough survey of the literature, Kast and Kolmer [14] conclude that it is highly doubtful if any investigator has succeeded in cultivating on artificial mediums virulent forms of S. pallida. In this opinion Plaut [15] and Jahnel [16] concur; indeed, Jahnel has failed not only with his own material but with cultures supplied him by other investigators who have claimed success. He was able to continue subcultures by various methods, but these were invariably avirulent.

Hoffmann and Frohn [17] claimed (alas, prematurely) that they had succeeded in obtaining pure cultures of S. pallida directly and immediately from closed testicular chancres of rabbits, utilizing Kroo's liquid nutritive medium. Subcultures were carried through five passages and were still virulent for rabbits at the end of that time. In a later paper, however, Hoffmann [18] joins the ranks of the skeptics and reports his

12. Gastinel, P., and Pulvenis, R.: Du rôle de la quantité de virus dans la syphilis expérimentale du lapin; la dose-seuil de l'infection inapparente, Bull. Soc. Franç. de dermat. et syph. **41**:330, 1934.

13. Morgan, H. J., and Thomas, C. S.: Single Cell Inoculations with T. pallidum, J. Exper. Med. **59**:297, 1934.

14. Kast, C. C., and Kolmer, J. A.: On the Cultivation of S. Pallida in Living Tissue Media, Am. J. Syph. & Neurol. **17**:529, 1933.

15. Plaut, F.: Ueber das Fehlen der antigenen Funktion der Gewebspallidae im Gegensatz zu der antigenen Wirksamkeit der in Reinkultur gezüchteten Syphilisspirochäten, Ztschr. f. Immunitätsforsch. u. exper. Therap. **81**:479, 1934.

16. Jahnel, F.: Untersuchungen über das Verhalten der Pathogenität von Spirochäten auf künstlichen Nährböden, insbesondere über die willkürliche Beeinflussung der Pathogenität von Hühnerspirochätenkulturen, Zentralbl. f. Bakt. (Abt. 1) **130**:349 (Dec. 29) 1933; Lässt sich die S. pallida auf künstlichen Nährboden kultivieren? Klin. Wchnschr. **13**:550, 1934.

17. Hoffmann, E., and Frohn, W.: Ueber Gewinnung einer direkten virulenten Reinkultur der S. pallida aus Kaninchensyphilom in flüssigem Nährboden, Klin. Wchnschr. **13**:206, 1934.

18. Hoffmann, E.: Gewinnung einer virulenten Reinkultur der Spirochaeta Pallida aus Kaninchensyphilom: Nachtag, Klin. Wchnschr. **13**:1540, 1934.

own inability to obtain further positive results with his original culture in generations later than the fifth, and also that he was not able to obtain further pure cultures from other closed syphilomas. He expresses the belief that his report of success in culturing virulent spirochetes was too hastily made and was a mistake, and agrees with those who believe that true cultures of S. pallida have never been obtained. Similar claims have from time to time been made by other investigators, beginning with Noguchi, the flaw being that on repetition in a different laboratory failure has always resulted.

THE CELLULAR PATHOLOGY OF SYPHILIS

Cunningham and his associates [19] in a series of stimulating papers have applied to the study of experimental syphilis the supravital method, which they previously employed with Sabin in studies on tuberculosis. They observed that the lesions of experimental syphilis in the rabbit contain higher numbers of phagocytic mononuclear cells (clasmatocytes, macrophages) and that the epithelioid cells present in tuberculous lesions are absent in syphilitic lesions. The clasmatocytes are much more numerous and much more phagocytic than in normal animals. It is apparently possible to increase still further the phagocytic activity of these cells in experimental animals by the intravenous administration of either trypan blue or lecithin. These substances, not in themselves spirocheticidal, nevertheless foster the resolution of syphilitic lesions in rabbits and inhibit the development of metastatic lesions. The authors suggest the hypothesis that the mechanism of resolution of syphilitic lesions may reside in the phagocytic activity of the large mononuclear cells of the tissues. It is hoped that this work will be continued, since it offers a new and promising theory of the pathologic aspects, course, progress and treatment of syphilis.

The Blood in Syphilis.—Spangler [20] observed moderate eosinophilia in the blood of approximately 40 per cent of his syphilitic patients. He believes that this indicates the development of an allergic cellular mechanism of defense. He also is of the opinion that in a nonallergic person without intestinal parasites the presence of a moderate degree of eosino-

19. Cunningham, R. S.; Morgan, H. J.; Tompkins, E. H., and Harris, S., Jr.: The Cellular Pathology of Experimental Syphilis as Studied by the Supravital Method, Am. J. Syph. & Neurol. **17**:515, 1933. Harris, S., Jr.; Tompkins, E. H.; Morgan, H. J., and Cunningham, R. S.: The Effect of Lecithin on Experimental Syphilis in the Rabbit, ibid. **18**:333, 1934. Morgan, H. J.; Harris, S., Jr.; Tompkins, E. H., and Cunningham, R. S.: The Effect of Trypan Blue on Experimental Syphilis in the Rabbit, ibid. **17**:522, 1933.

20. Spangler, R. H.: Eosinophilia in Syphilis: Comparative Study of Differential Leucocyte Counts in One Hundred Positive and One Hundred Negative Blood Wassermann Cases, J. Lab. & Clin. Med. **20**:733, 1935.

philia, especially if associated with lymphocytosis, should serve as a diagnostic suggestion of the presence of syphilis and should prompt careful search for clinical and laboratory evidence of syphilis.

Continuing the studies of Cunningham and his associates on the essential cellular response of the blood and tissues in experimental syphilis, Lowenstein [21] has studied the leukocytic formula in the early acute stage of experimental syphilis in rabbits. He observed an increase in the number of phagocytic mononuclear cells, which qualitatively showed evidence of increased physiologic and phagocytic activity. There was also a decrease in the number of lymphocytes. The degree of increase of the phagocytic mononuclear cells paralleled the degree of activity at the site of the testicular lesions. No significant changes were observed in the total number of leukocytes or in other elements of the differential blood count.

In a series of papers Rosahn, Pearce and Casey [22] report their studies of the cytology of the blood of syphilitic animals and human beings. In rabbits during the period of active disease there was an increase in the total leukocyte count and in the number of neutrophils, monocytes and platelets and a decrease in the number of lymphocytes. During the period of latency these changes in the leukocytes disappeared, but a mild secondary anemia developed. There is a distinct parallelism between these observations and those made on human beings. In early syphilis in human beings there are mild leukocytosis; an increase in the number of monocytes, neutrophils and platelets and a decrease in the number of lymphocytes. In late syphilis these changes disappear, but a moderate or marked anemia is frequently observed. All these changes tend to disappear following treatment.

SEROLOGY

The American Serologic Conference.—Under the combined auspices of the United States Public Health Service and the American Society of Clinical Pathologists a competitive conference of American serologists has just been held [23] for the purpose of determining the reliability

21. Lowenstein, L.: The Leucocytes in Early Acute Experimental Syphilis in Rabbits, Am. J. Syph. & Neurol. **19**:39, 1935.

22. Rosahn, P. D., and Pearce, L.: The Blood Cytology in Untreated and Treated Syphilis, Am. J. M. Sc. **187**:88, 1934. Rosahn, P. D.; Pearce, L., and Casey, A. E.: Observations on the Blood Cytology in Experimental Syphilis: I. The Period of Disease Activity, J. Exper. Med. **59**:711, 1934. Rosahn, P. D.: Observations on the Blood Cytology in Experimental Syphilis: II. The Period of Disease Latency, ibid. **59**:721, 1934.

23. Cumming, H. S.; Hazen, H. H.; Sanford, A. H.; Senear, F. E.; Simpson, W. M., and Vonderlehr, R. A.: Evaluation of Serodiagnostic Tests for Syphilis in the United States, J. A. M. A. **103**:1705 (Dec. 1) 1934; Evaluation of Serodiagnostic Tests for Syphilis in the United States: Report of Results, ibid. **104**:2083 (June 8) 1935.

of the several serodiagnostic methods that are in common use in this country. The conference was organized in the same manner as earlier international competitions in Europe and South America, except that in this instance the participating serologists worked in their own laboratories rather than in a central place. Twelve hundred specimens of blood and of spinal fluid from carefully selected donors were examined under identical conditions by fourteen participating serologists, four of whom (Brem, Kolmer, Ruediger and Williams) performed some modification of the complement-fixation (Wassermann) test and ten of whom (Eagle, Hinton, Johns, Kahn, Kline, Kurtz, Lufkin and Rytz, Rein and Weiss) performed a flocculation test. Detailed descriptions of the technic employed by each of these workers will appear in a subsequent communication. Specimens of blood were submitted (1) from patients with untreated primary syphilis, (2) from patients with untreated secondary syphilis, (3) from patients with late syphilis both treated and untreated, (4) from normal, presumably nonsyphilitic persons and (5) from presumably nonsyphilitic patients with leprosy, tuberculosis, cancer, fever, malaria and jaundice, pregnant women and normal women both during menstruation and in the interim. Samples of spinal fluid were submitted in equal numbers from neurosyphilitic and nonsyphilitic patients.

The conference scored the tests of the competing serologists on two bases: (1) sensitivity, i. e., the proportion of positive results in about 400 patients with known syphilis, and (2) specificity, i. e., the percentage of false positive (not including false doubtful) reactions secured in 152 presumably normal controls. I believe, however, that specificity might be more accurately determined if there were added to the 152 normal controls the approximately 300 presumably nonsyphilitic persons with the other conditions listed in the preceding paragraph (excluding, for reasons which will presently appear, leprosy and malaria) and if to false positive results in this heterogeneous group were also added false doubtful reactions (which can cause as much confusion in the mind of the clinician). Refigured on this basis the most satisfactory tests on both scores, i. e., sensitivity and specificity, were the complement fixation (Wassermann) test performed by Ruediger and the Kline diagnostic flocculation test as performed by Kline. A close second was the standard diagnostic Kahn flocculation test as performed by Kahn. Equally close thirds were the Eagle flocculation test and the Kahn presumptive flocculation test (Kurtz). The others were relatively unsatisfactory on one score or the other.

It is of interest to note that in specimens from presumably nonsyphilitic patients with leprosy or malaria all of the competing serologists obtained a significantly higher proportion of positive results than in specimens from patients with other nonsyphilitic conditions. In speci-

mens from persons with leprosy the percentage of positive results ranged from 44 to 72, and in those from persons with malaria, from 8 to 20. It seems reasonable to conclude, therefore, that leprosy often and malaria occasionally may cause a false positive serologic test for syphilis. The uniformity of the results should aid in settling the controversy that has raged around the question in these two diseases.

The evaluating committee state as their conclusion that there is relatively equal value to the clinician of efficient complement-fixation and efficient flocculation tests as performed on specimens of either blood or spinal fluid. If two tests are performed as an intralaboratory check, it is immaterial whether two complement-fixation tests, two flocculation tests or one of each is chosen. There is some evidence that a properly performed highly sensitive flocculation test might be used as a routine procedure for the purpose of excluding the likelihood of the presence of syphilis. If a negative result is obtained by such a method, it is likely that it will be negative by any other method. If the test yields a positive result, it should be repeated and compared with one or more highly specific flocculation or complement-fixation tests. The committee recommend the uniform adoption of the words positive, doubtful and negative in reporting tests in place of the various plus marks at present in common use.

The Relationship Between Serologic Tests of the Blood and Those of the Spinal Fluid.—The routine use of lumbar puncture during the treatment of patients with early and late syphilis is insisted on by all modern American syphilologists. Asymptomatic neurosyphilis is common; it is the forerunner of subsequent clinical involvement; abnormalities of the cerebrospinal fluid may be present when the Wassermann reaction of the blood is negative. These abnormalities do not depend on the passage of reagin from the blood to the spinal fluid but are elaborated locally in the nervous system, and in the experience of most serologists and clinicians no serologic test of the blood has as yet been devised that is so sensitive as to be always positive when the cerebrospinal fluid is abnormal. It is unfortunate, therefore, that on the basis of insufficient evidence Hinton [24] claims that the test which he has devised is sufficiently sensitive. On the basis of studies of only 50 patients with early syphilis for whom both Hinton tests and examinations of the cerebrospinal fluid were made at the same time, he concludes that in order to demonstrate the presence of asymptomatic neurosyphilis lumbar puncture is not necessary during the first two years of the disease, since in his patients the examinations of the spinal fluid and the Hinton tests were negative in 20 instances and no positive reac-

24. Hinton, W. A.: Hinton Test and Lumbar Puncture in Treated Primary and Secondary Syphilis, Arch. Dermat. & Syph. **30**:813 (Dec.) 1934.

tion of the spinal fluid was observed when the Hinton test was negative, though in 2 such instances the results of the tests of the spinal fluid were doubtful. His conclusion is obviously unjustified on the basis of such meager data, and the publication of this paper may do a great deal of harm by persuading uncritical physicians that a study of the cerebrospinal fluid is unnecessary.

Cerebrospinal Fluid.—Solomon, Dailey and Fremont-Smith [25] present a valuable study and simple formulas whereby a reasonably accurate cell count, values for protein, sugar and chloride content and colloidal reactions may be obtained on cerebrospinal fluid that has been accidentally contaminated with blood.

The Kahn test on the cerebrospinal fluid was found by Loveman and Stocking [26] to be unreliable when as little as 0.0018 cc. of blood serum giving a strongly positive Kahn reaction was added to 6 cc. of spinal fluid. These authors conclude that if the Kahn test of the cerebrospinal fluid is positive and the fluid has been contaminated with blood, another lumbar puncture should be done. It has been my experience with the Wassermann test, however, that this precaution is often unnecessary if the quantitative Wassermann titer of the blood serum at the time of the lumbar puncture is known.

The Luetin Test and Cutaneous Allergy in Syphilis.—After the introduction of the luetin test by Noguchi in 1911, a controversy as to its value ensued. This controversy died down when the original test was shown to be of no practical value but was renewed with the relatively recent interest in "organic luetin." The latest careful study by Barker [27] shows once more that luetin of any type is of no practical value in diagnosis or as a determination of cure. Its status in treatment is not settled, but its value is not great.

Bessemans, Dujardin and Wiser [28] have conducted a more elaborate and better controlled study of several extracts of luetin which they have prepared. Their conclusions are of great interest to the student of the influence of immunity and of constitution in determining the response to syphilitic infection. Cutaneous reactivity to these various extracts is at its height in patients with allergic lesions of tertiary syphilis and at

25. Solomon, P.; Dailey, M. E., and Fremont-Smith, F.: Contamination of the Cerebrospinal Fluid by Blood, Arch. Neurol. & Psychiat. **31**:1222 (June) 1934.

26. Loveman, A. B., and Stocking, L.: Kahn Reaction with Spinal Fluids Containing Varying Amounts of Syphilitic Blood, Arch. Dermat. & Syph. **29**:653 (May) 1934.

27. Barker, L. P.: Value of Organic Luetin in Diagnosis and Treatment of Syphilis, Arch. Dermat. & Syph. **30**:676 (Nov.) 1934.

28. Bessemans, A.; Dujardin, B., and Wiser, M.: Sur l'hypersensibilité cutanée des syphilitiques, Ann. de dermat. et syph. **4**:1010, 1933.

its minimum in those with parasyphilis (i. e., parenchymatous neurosyphilis). It may be shown in response to the intradermal injection of not only extracts of luetin but of various protein products, such as horse serum or cow's milk. It is more striking in women than in men, corresponding to the milder course of syphilis in women. These workers agree, however, that skin testing of this sort is of no value in diagnosis. To me it seems to offer a prolific field for further investigation with regard to immunity and constitution in order to determine the probable course of syphilis in a freshly infected person.

THE EPIDEMIOLOGY OF SYPHILIS

Usilton [29] provides a valuable summary of the surveys that have been made of the prevalence of venereal disease in recent years by the United States Public Health Service and the American Social Hygiene Association with the cooperation of state and local health authorities. Forty-nine representative communities, with a total population of approximately 29,000,000 persons, are included. As far as syphilis is concerned, there are constantly under medical care for this disease 4.3 persons per thousand population, an approximate total of 683,000 persons. The annual incidence of fresh infections with syphilis is 4 per thousand. The trend of the incidence of syphilis appears to be upward, with a possible 3.4 per cent increase during the past period of from three to six years.

In contrast to this gloomy state of affairs in this country is the fact that in Denmark syphilis is disappearing. In 1933 only 700 fresh infections occurred in the entire country (population of 3,500,000), an incidence rate of 0.2 per thousand. Had the incidence rate in Denmark been the same as in the United States, 14,000 new cases would have been reported instead of a mere 700. The measures which epidemiologists agree have accomplished this striking decrease in incidence are described in illuminating papers by Kissmeyer [30] and Lomholt.[31]

Smith and Brumfield [32] have provided a useful demonstration of the practicability and value of tracing the sources of contact of persons infected with syphilis. This type of "shoe leather" epidemiology is of the highest importance from the standpoint of public health.

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29. Usilton, L. J.: Trend of Syphilis and Gonorrhea in the United States, Based on Treated Cases, Ven. Dis. Inform. **16**:147, 1935.

30. Kissmeyer, A.: Sur la quasi-disparition de la syphilis au Danemark, Bull. Soc. franç. de dermat. et syph. **40**:926, 1933.

31. Lomholt, S.: Rückgang der Syphilis in Dänemark 1919-1933, Dermat. Wchnschr. **100**:173, 1935.

32. Smith, D. C., and Brumfield, W. A., Jr.: Tracing the Transmission of Syphilis, J. A. M. A. **101**:1955 (Dec. 16) 1933.

DRUGS

Mercury.—Sollmann, Schreiber, Cole and their collaborators [33] have continued their studies on the absorption and excretion of mercury. The important conclusions are found in the second paper cited. The antisyphilitic efficiency of mercurial treatment appears to be conditioned on the continued maintenance of an adequate concentration of diffusible, dissociable mercury. The mercury that is fixed and stored in the tissues appears to play no therapeutic rôle. The urinary excretion of mercury serves as an indicator of the presence of diffusible mercury. With therapeutically effective preparations and routes of administration, excretion is continuously cumulative. All forms of treatment yielding levels below 0.5 mg. of mercury per day at the end of the fourth week are clinically ineffective. These include inunction with ointments of mild mercurous chloride and with weak (5 per cent) ointments of metallic mercury and mercury oleate; oral administration of mercuric chloride in doses of 15 mg. per day; intravenous injection of the oxycyanide and intramuscular injection of the benzoate in the usual dosage; intermittent intramuscular injection of biniodide, and intravenous injection of compounds with their mercury in firm organic combination—salyrgan, novasurol and mercurosal. These give very high temporary levels for the excretion of mercury, but they sink to insignificant ones within a few hours. All methods of treatment which secure a daily urinary excretion of from 0.8 to 1 mg. of mercury at the end of the fourth week are effectively antisyphilitic and may cause stomatitis. The ordinary and the massive inunctions, the daily oral administration of 0.2 Gm. of mercury with chalk, the daily intramuscular injection of mercuric sodium bromide and the weekly intramuscular injection of mercuric oil come within this group. With the last preparation there is the constant danger of cumulative intermittent absorption and intoxication. All of these methods, however, may be dangerous. Considerable quantities of mercury are retained in the body indefinitely, but this retained mercury is therapeutically useless and may be harmful.

These studies represent an enormous amount of painstaking careful work. It seems regrettable that this effort is robbed of much of its importance by the nearly complete abandonment of mercury in favor of bismuth in clinical practice.

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33. Sollmann, T.; Schreiber, N. E.; Cole, H. N., and others: Excretion of Mercury After Oral Administration of Mercury with Chalk, Yellow Mercurous Iodide and Corrosive Mercuric Chloride, Arch. Dermat & Syph. **31**:15 (Jan.) 1935; Excretion of Mercury After Clinical Intramuscular and Intravenous Injections, ibid. **32**:1 (July) 1935.

Bismuth.—In a comprehensive review documented by a bibliography of 204 references, Levaditi [34] brings up to recent date (1932) the status of bismuth in the treatment and prophylaxis of syphilis. He covers the history of the drug, enumerates and describes the preparations in common use in the United States as well as abroad, and considers toxicity, tolerance, the pathogenesis and pathology of bismuth intoxication, the absorption of bismuth and its distribution in the tissues, the therapeutic effect and mechanism of its action, the accidents and reactions of bismuth therapy and the prophylaxis of syphilis by means of this drug.

He favors for clinical use the liposoluble alpha-carboxethyl-beta-methylnonoate (marketed in this country as biliposol), which he says acts almost as rapidly as the arsphenamines; and he makes the assertion, with which few investigators outside France will agree, that syphilis can be treated exclusively with this drug, with results equivalent to those obtainable with the arsphenamines.

Bismuth Prophylaxis of Syphilis.—In 1926 Kolle and Evers reported interesting experiments in which they injected the very insoluble bismuth oxychloride into a rabbit's ear or thigh and then a few days later inoculated the animal intratesticularly with syphilitic virus. They observed the animals over a period of several months, and no chancre appeared. Then they surgically removed the remaining deposit of bismuth, whereupon a chancre promptly developed at the point of inoculation. They therefore concluded that the action of bismuth was spirochetistatic rather than spirocheticidal; i. e., it prevented the growth of the virus rather than destroyed it. This important work had not been repeated until Levaditi and his collaborators [35] undertook it. They demonstrated that when insoluble metallic bismuth was used it was impossible to administer to rabbits an adequate prophylactic dose capable of complete surgical removal, but when a liposoluble salt was employed the animals were completely protected against infection, both before and after the surgical removal of the deposit of bismuth. This protection was manifest by the absence of a chancre at the site of inoculation, by negative results of the transfer of material from the lymph nodes and by the ultimate susceptibility of the animals (after removal of all the bismuth either surgically or by normal excretory processes) to reinoculation. They conclude that when bismuth is given in adequate form and in sufficiently large doses it is actually spirocheticidal rather than spirochetistatic. The

34. Levaditi, C.: Etat actuel de la bismuthothérapie et de la bismuthoprévention de la syphilis, Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap. **14:** 297, 1933.

35. Levaditi, C.; Hornus, G.; Vaisman, A., and Manin, Y.: Mécanisme de l'action préventive exércée par le bismuth dans la syphilis expérimentale, Bull. Acad. de méd., Paris **112:**306, 1934.

different results obtained by Kolle and Evers are apparently due only to the extreme insolubility and low absorbability of the bismuth preparation which they employed.

Oral Administration of Bismuth.—In a series of four papers Serefis and Mulzer [36] discuss the treatment of syphilis by the oral administration of bismuth. In the first paper of the series Serefis describes the manifestations of acute and chronic bismuth poisoning and presents the results of some experiments dealing with the solubility and absorbability of different bismuth preparations. In a rather confused presentation he states that he finally settled on bismuth chloride as a suitable salt for oral administration. This preparation is completely soluble in an acid medium, but this medium is too acid for ingestion. Its relative insolubility in an alkaline medium can be overcome by the addition of certain salts, alcohols or sugars which, in the author's opinion, combine with the bismuth chloride to form complex salts of an undetermined nature.

The second paper deals with the treatment of experimental syphilis in rabbits with various bismuth compounds given by mouth. Acid bismuth chloride in glycerin was effective in rabbits when three doses of 0.172 Gm. of metallic bismuth was given. Unfortunately, the number of animals treated was small (only 7), the dosage is not expressed in milligrams per kilogram of body weight, the intervals between multiple doses are not given, the period of observation of the animals was inadequate and "cure" of the animals was not checked by the transfer of glandular tissue. In spite of these inadequate data, several patients with early syphilis were treated with a mixture of bismuth chloride, sodium citrate and glycerin in a daily dose of 0.8 Gm. of metallic bismuth, with what Serefis considered as encouraging results.

Next, in a long paper, Serefis supplies more but still inadequate details of his own experimental work. In addition to the deficiencies in his protocols that have been noted, his work is still further subject to serious criticism on the ground that he does not describe the proportions used in the most effective preparation tried, i. e., bismuth chloride plus sodium citrate plus glycerin.

On the basis of these observations, which if adequate to convince the investigators of the value of the method are so inadequately presented as to leave the reader greatly confused, Mulzer and Serefis proceeded

36. Serefis, S.: Die perorale Wismutvergiftung, Med. Klin. **30**:968, 1934; Die Resorptionsbedingungen des Wismut vom Magen-Darmkanal aus, Deutsche med. Wchnschr. **60**:1237, 1934; Ueber die Resorptionsbedingungen des Wismut und ihre Auswertung für die perorale Luestherapie, Arch. f. Dermat. u. Syph. **171**:1, 1934. Mulzer, P., and Serefis, S.: Die perorale Wismutbehandlung der Syphilis, München. med Wchnschr. **81**:1525, 1934.

further. They treated bismuth chloride with 8 per cent liver extract (the method is not described) and obtained a substance not chemically identified but which they believed to be a complex bismuth salt, to which they gave the name "bismutrat." If the authors tried this substance on experimental animals, they do not mention it in their papers. (The manufacturers, however, state that the action of "bismutrat" in rabbits with experimental syphilis is inferior to that in human beings because of the alkaline state of the complex salt.) In spite of the absence of adequate experimentation on animals, Mulzer and Serefis used this substance on 43 patients with syphilis (13 had primary and 24 secondary syphilis). The average daily dose was from 25 to 40 Gm., thirty doses constituting a course. None of the patients died of bismuth poisoning. According to the authors, surface organisms disappeared, lesions healed and reversal of the Wassermann reaction occurred with great rapidity.

I have discussed these articles in detail because of the authority represented by the authors' names, because unjustified clinical trial preceded adequate experimentation (or at least adequate presentation of that experimentation) and because, on the basis of thoroughly inadequate evidence of the value of the method or the preparation employed, commercial distribution of "bismutrat" has already begun abroad and may shortly occur in this country.

Considerable interest in this subject has been aroused in this country also. Kolmer [37] reports on the oral use of water-soluble potassium bismuth tartrate in experimental animals and man. Unfortunately, his paper is devoid of protocols of his experimental work, and the reader must rely on statements only. This is, of course, a most unsatisfactory method of presentation of an important scientific subject. However, if one accepts Kolmer's statements at their face value, they are as follows: Rabbits tolerated without obvious damage fifty consecutive daily oral doses of 20 mg. (approximately 8 mg. per kilogram), rats tolerated 5,000 mg. per kilogram, given in a single dose; the daily dosage employed for adult human beings was from 0.57 to 1.2 Gm. Syphilis was apparently cured in rabbits by twenty-four daily doses of 20 mg. per kilogram. Kolmer states that he has used this method of treatment in human beings for ten years, that the bismuth compound administered orally gives better results than mercury salts given in the same manner and that there are definite indications for the use of the method in human beings.

Neither the work of Mulzer and Serefis nor that of Kolmer can as yet be accepted as justifying a clinical trial of this method. Too many details of both experimental and clinical results are lacking in the reports of these observers. It is to be hoped that the entire subject will be

37. Kolmer, J. A.; Oral Administration of Potassium Bismuth Tartrate in Treatment of Syphilis, Arch. Dermat. & Syph. **31**:9 (Jan.) 1935.

critically restudied, with more careful and adequate reports of the results obtained.

Bismuth in the Central Nervous System.—Much of the commercial propaganda for iodobismitol has stressed the supposed power of the preparation to penetrate the nervous system and the consequent desirability of its use in neurosyphilis. The contrary results reported by Levaditi and his associates [38] are therefore of interest. They observed that both in therapeutic efficacy in rabbits with syphilis and in its power to penetrate the nervous system and invade the cerebrospinal fluid, iodobismitol is equal, but not superior, to other liposoluble bismuth preparations.

The excretion of iodobismitol is shown by Hanzlik, Mehrtens and Spaulding [39] to be largely by way of the urine and in amounts comparable to those following the use of water-soluble bismuth salts. Klauder and Brown [40] utilize these facts, together with their own failure to demonstrate an increased concentration of bismuth, in the cerebrospinal fluid of human beings and in the brains of experimental animals after the administration of iodobismitol as compared with other bismuth preparations, to refute the argument of Hanzlik and his co-workers that the particular penetrating power of iodobismitol is due to the existence of bismuth in the anionic form.

The Iodides.—Greenbaum and Cobane [41] express the opinion that the only effect of the iodides in syphilis is in dissolving syphilitic exudates and incompletely organized fibroses, that these effects are better accomplished by arsenical or bismuth compounds and that there is evidence to suggest that the iodides are not indispensable in the treatment of syphilis irrespective of the stage or manifestation. While this opinion is based on hypothesis rather than on observed facts, it is identical with the point of view of other syphilologists and constitutes a useful critical approach to the existing uncertainties of antisyphilitic treatment. The actual demonstration of the lack of value of the iodides (except in providing symptomatic relief) is difficult if not impossible.

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38. Levaditi, C.; Vaisman, A.; Manin, Y., and Schoen, R.: La diffusion du bismuth dans le névraxe et sa pénétration dans le liquide céphalo-rachidien, Bull. Soc. franç. de dermat. et syph. **40**:738, 1933.

39. Hanzlik, P. J.; Mehrtens, H. G., and Spaulding, J. B.: Iodobismitol: Clinical Excretion of Bismuth, Arch. Dermat. & Syph. **29**:298 (Feb.) 1934.

40. Klauder, J. V., and Brown, H.: Question of Bismuth Penetration of the Nervous System: Report of Clinical and Laboratory Study, Arch. Dermat. & Syph. **29**:351 (March) 1934.

41. Greenbaum, S. B., and Cobane, J.: Syphilitic Fibrosis and the Status of the Iodides in the Present Day Treatment of Syphilis, Am. J. Syph. & Neurol. **18**:289, 1934.

TOXIC REACTIONS DUE TO DRUGS

The Effect of Antisyphilitic Treatment on Renal Function.—Sézary and Lenègre [42] have studied the renal function of 50 untreated patients with secondary syphilis, and in 32 of these patients they have repeated the examinations after three courses of treatment with various drugs, including neoarsphenamine, insoluble and oil-soluble bismuth and mercury. In addition to careful and repeated examinations of the urine, the excretion of phenolsulphonphthalein and Ambard's constant were studied in each case. In their series of patients neither syphilis nor antisyphilitic treatment produced any evidence of impairment of the renal function, though during treatment of any sort abundant hyaline casts could be found in the urine of almost every patient. In an additional 60 patients who had been receiving antisyphilitic treatment for periods ranging from one and a half to sixteen years, similar examinations carried out *after* (but not controlled by examinations *before* and *during*) treatment revealed in some patients the presence of mild nephritis, but it could not be clearly connected with the antisyphilitic treatment.

Ocular Damage Due to Arsphenamine.—In spite of earlier controversy on the point, recent opinion has held that although the pentavalent arsenical drugs (sodium arsanilate, tryparsamide) may produce damage to the optic nerves, the trivalent arsphenamines never do. That this opinion deserves restudy is evident from the interesting report of Skirball and Thurman.[43] These workers observed that in 20 patients, 19 of them with early syphilis, optic neuritis developed following the administration of an arsphenamine. In some patients there were retinal hemorrhages, haziness of the vitreous and central scotomas. The authors express the opinion that the condition can be readily differentiated from the neuroretinitis of acute meningeal neurosyphilis, though they do not describe the differential points. None of their patients showed any other evidence of neurosyphilis, and in the only 3 cases tested the cerebrospinal fluid was normal. They state that the reaction occurred in the surprisingly high total of 2.7 per cent of all patients with early syphilis who were treated. The first signs are usually subjective and unilateral. Objective evidence of haziness of the vitreous or blurring of the nerve head, either absent or slight at the onset of symptoms, occurs within

42. Sézary, A., and Lenègre, J.: Le fonctionnement rénal des syphilitiques secondaires; l'action du traitement d'attaque sur le fonctionnement rénal des syphilitiques secondaires; l'action des traitements antisyphilitiques prolongés sur la fonctionnement rénal, Bull. et mém. Soc. méd. d'hôp. de Paris **49**:1278, 1280 and 1287, 1933.

43. Skirball, J. J., and Thurman, F. M.: Ocular Reactions Due to Arsphenamine, Am. J. Syph. & Neurol. **19**:197, 1935.

from a few days to two weeks. If the use of arsphenamine is continued after the reaction first appears, the condition grows progressively worse, resulting in severe optic neuritis and ending in secondary atrophy. On the other hand, if the use of arsphenamine is discontinued there is prompt improvement and in most instances complete recovery. In some instances (2 cases are cited) the same condition may be reproduced after recovery by the further administration of arsphenamine. A somewhat similar case is reported by Juler.[44]

These reports are, of course, completely contrary to the experience of syphilologists and ophthalmologists the world over. While neuroretinitis does occur during or after the inadequate treatment of early syphilis (almost never in late syphilis), it has been interpreted by most observers as an ocular recurrence or neurorecurrence that is frequently associated with abnormalities in the spinal fluid that are typical of syphilis and can be cured rapidly by the administration of more arsphenamine, not by its withdrawal. It seems incredible that for twenty-five years many competent observers in clinics where this point of view prevails could have failed to note the presence of optic neuritis followed by secondary optic atrophy in 2.5 per cent of all patients with early syphilis treated with arsphenamine. Nevertheless, the subject is deserving of further careful study.

Hemorrhagic Encephalitis Due to Arsphenamine.—Glaser and the Imermans [45] report 3 of their own cases on hemorrhagic encephalitis due to arsphenamine and analyze 155 instances cited in the literature (unfortunately, the bibliography is provided only in the author's reprints). They conclude that reactions involving the nervous system appear about once in every 5,400 patients treated and once in every 29,000 injections. (On the basis of my own experience, I believe that these figures are much too high.) The mortality is about 75 per cent. The appearance of the reaction is not related to the age or sex of the patient, to the stage of the disease or to the dose of the drug. The onset of symptoms is usually from twelve hours to six days following treatment and usually early in the course of treatment. The outstanding symptoms are headache, vomiting, nervousness, chills and vertigo, with physical signs of fever, cyanosis, convulsions, changes in the pupillary reflexes and in the ocular muscles, loss of sphincteric control, hemiparesis and rigidity of the neck. The pressure of the spinal fluid is usually increased, and there is often concomitant acute nephritis. Therapy is unsatisfactory.

44. Juler, F.; Blindness After Neoarsphenamine, Brit. M. J. **2**:809, 1934.

45. Glaser, M. A.; Imerman, C. P., and Imerman, S. W.: So-Called Hemorrhagic Encephalitis and Myelitis Secondary to Intravenous Arsphenamine, Am. J. M. Sc. **189**:64, 1935.

In reporting 3 cases of this grave complication of treatment in pregnant women Plass and Woods [46] point out that this (and certain other serious reactions to arsphenamine) are more prone to occur in pregnant women than in other subjects.

Chetverikov and Kavyrshin [47] add reports of 3 cases of hemorrhagic encephalitis to the already voluminous literature on this subject. Their report is chiefly remarkable for the fact that all 3 of their patients survived and for some bizarre theorizing as to the relationship of this reaction to defective functioning of the vegetative endocrine apparatus, the hemato-encephalic barrier and menstruation.

Osterberg and Kernohan [48] have observed arsenic in the brain in relatively large amounts in patients with hemorrhagic encephalitis due to arsphenamine.

Toxic Hepatitis Due to Arsphenamine.—Wile and Sams [49] provide the most recent thorough review of this important topic on the basis of 65 personally observed patients. Jaundice due to treatment developed in 1.3 per cent of the patients treated in their clinic. All the arsenical drugs employed, including tryparsamide, were about equally responsible. Dosage was not a factor. The hepatitis occurred from one to one hundred and thirty-nine days after the last treatment, with early (fifth day) and late (about the ninety-fifth day) peaks. The cause of the reaction is not clear. The authors do not subscribe to the French view that it is due to syphilis of the liver (hepatorecurrence) and state that they feel that there is inadequate chemical evidence to justify the theory that the toxic action is due to retention of arsphenamine in the liver. Chemical studies supporting this theory are lacking. On the whole, the authors favor the theory that the disease is related in some manner to epidemic infectious jaundice. This is supported by the clinical course, which is indistinguishable from so-called acute catarrhal jaundice, and by epidemiologic data. However, necropsy observations in the fatal cases of acute yellow atrophy following the use of arsphenamine indicate that the icterus results from severe intoxication and destruction of the hepatic substance analogous to other forms of poisoning which lead to acute yellow atrophy. Until more accurate means are at hand for the determination of susceptibility to arsphenamine and of hepatic function and until the drug is modified to make it less hepatotoxic, jaundice

46. Plass, E. D., and Woods, E. B.: Hemmorrhagic Encephalitis (Neoarsphenamine) in Obstetric Patients, Am. J. Obst. & Gynec. **29**:509, 1935.

47. Chetverikov, N. S., and Kavyrshin, A. Y.: Symptoms of Lesions of Spinal Cord Following Neoarsphenamine Injections, Klin. med. **12**:1374, 1934.

48. Osterberg, A. E., and Kernohan, J. W.: Presence of Arsenic in the Brain and Its Relation to Pericapillary Hemorrhages or So-Called Acute Hemorrhagic Encephalitis, Am. J. Clin. Path. **4**:362, 1934.

49. Wile, U. J., and Sams, W. M.: A Study of Jaundice in Syphilis: Its Relation to Therapy, Am. J. M. Sc. **187**:297, 1934.

due to arsphenamine will continue to be among the severe complications of the modern treatment of syphilis.

Baldridge [50] offers the disquieting suggestion that antisyphilitic treatment may be responsible for cirrhosis of the liver. He reports the cases of 12 patients with portal cirrhosis, none of whom had had either syphilis of the liver or postarsphenamine jaundice, but all of whom had received antisyphilitic treatment (in at least 10 instances including an arsphenamine) usually within from six to eight months preceding the development of the hepatic symptoms. In no instance was clinical evidence of disease of the liver found before the antisyphilitic treatment was begun. In 3 of 4 patients who came to necropsy the cirrhosis was of the toxic type (i. e., the result of a previous acute yellow atrophy), an observation which seems strange in view of the author's definite statement that "in no case was there a history of post-arsphenamine jaundice, and no symptom which would suggest a non-fatal acute yellow atrophy of the liver was observed while the patients were under treatment." Although Baldridge's observations are foreign to the experience of most observers, his remarks should prompt additional study of this important question.

Postarsphenamine Dermatitis.—Shaffer [51] summarizes current opinion and practice with regard to the treatment of the distressing complication, postarsphenamine dermatitis. He still holds that sodium thiosulphate is of some value, especially if used early, in spite of the fact that no experimental evidence supports this view and that the clinical evidence is far from convincing. He reviews the literature on the use of liver extract and of calcium salts, both of which have been employed empirically by various observers and with varying success. Of most value, he says, is the intravenous administration of dextrose (50 cc. of a 50 per cent solution daily for from three to five days). The chief tangible rationale of this method of treatment lies in the hypothesis that the glycogenic function of the liver is disturbed during postarsphenamine dermatitis (which hypothesis, incidentally, has not been proved), in the supposed influence of the dehydrating effect of dextrose in promoting the transfer of toxic substances from tissue to blood and hence to excretory organs (also not proved for arsphenamine or its split products) and in the fact that dextrose added to solutions of arsphenamine before their administration lowers their toxicity. Other less tangible hypotheses are also offered in support of the idea. The clinical impressions of the author and of several discussers of his paper were all favorable to this method of treatment, which, as may be seen, still rests on an unsatisfactory empirical basis. Too little is known of the exact mechanism

50. Baldridge, C. W.: The Relationship Between Antisyphilitic Treatment and Toxic Cirrhosis, Am. J. M. Sc. **188**:685, 1934.

51. Shaffer, L. W.: Treatment of Postarsphenamine Dermatitis, Arch. Dermat. & Syph. **29**:173 (Feb.) 1934.

of the production of arsphenamine dermatitis to permit the development of an entirely rational treatment.

The Determination of Arsphenamine Sensitivity by Patch and Intravenous Testing.—Some varieties of postarsphenamine dermatits are expressions of permanent sensitization, while others are not; and in the former group the sensitization is sometimes drug-specific rather than group-specific. These facts make it important to determine in certain patients whether sensitization to a specific member of the arsphenamine series persists, preventing the further use of any of these drugs. Jordan and Osborne [52] take the same position as Robinson,[53] namely, that the patch test is not a reliable guide to further treatment with arsphenamine following recovery from arsphenamine dermatitis and that the only safe method of determining whether more arsphenamine can be tolerated by such patients is by the intravenous administration of minute, gradually ascending doses of the drug in question.

Cannon and Karelitz,[54] in an article that is longer than the relative importance of the subject justifies, conclude that the intradermal test for arsphenamine sensitivity is, like the patch test, unsatisfactory since it is often negative in patients known to be sensitive and sometimes positive in patients known not to be sensitive.

The conclusions stated in these three papers are in direct contradiction to the work of Schoch,[55] who says that the patch test is sufficiently reliable to be employed as a guide in treatment. My personal experience leads me to join the majority in their opinion that the patch and intradermal tests are of no practical value.

The Treatment of Heavy Metal Poisoning.—In view of the apparently complete inefficacy of sodium thiosulphate and of calcium preparations in the treatment of arsphenamine dermatitis and jaundice (most recently reported on by Keim [56]), the success reported by Rosenthal [57] in

52. Jordan, J. W., and Osborne, E. D.: Observations on Arsphenamine Dermatitis, with Especial Reference to the Reliability of the Patch Test, New York State J. Med. **35**:210, 1935.

53. Robinson, H. M.: Patch Tests in the Determination of Arsphenamine Sensitivity, South. M. J. **27**:845, 1934.

54. Cannon, A. B., and Karelitz, M. B.: Intradermal Tests in Relation to Arsphenamine Dermatitis, Arch. Dermat. & Syph. **29**:485 (April) 1934.

55. Schoch, A. G.: Arsphenamine Dermatitis: Attempted Sensitization to Neoarsphenamine and Further Observations on the Patch Test, Arch. Dermat. & Syph. **30**:672 (Nov.) 1934.

56. Keim, H. L.: "Erythema of the Ninth Day" Following Administration of Arsphenamine: Preliminary Report, Arch. Dermat. & Syph. **31**:291 (March) 1935.

57. Rosenthal, S. M.: Experimental Studies on Acute Mercurial Poisoning, Pub. Health Rep. **48**:1543, 1933; An Antidote for Acute Mercury Poisoning, J. A. M. A. **102**:1273 (April 21) 1934.

the treatment of mercury poisoning in experimental animals and man by means of sodium formaldehyde sulphoxylate is of interest. Unfortunately, Brown and Kolmer [58] were unable to confirm Rosenthal's results in animals. In order to save rabbits poisoned with mercury the antidote had to be administered within an hour after the mercury had been administered.

THE USE OF MALARIA IN THE TREATMENT OF DRUG-RESISTANT SYPHILIS

In a very brief paper Dennie and McBride [59] point out the value of malaria therapy in patients with either early or late syphilis whose lesions fail to heal under the ordinary drug therapy. They express the belief that the etiologic factor in such cases is not the inefficacy of the drugs employed but the failure of the defense mechanism of the body. The effect of malaria is to reactivate the defense mechanism and to enhance the value of subsequent treatment. I have had identical experiences, hold identical beliefs and regret that the authors did not present these important facts in greater detail.

CEREBROSPINAL FLUID

Headaches Following Lumbar Puncture.—In one paper of an interesting series on intracranial hydrodynamics, Masserman [60] proposes a relatively new explanation for severe postpuncture headache. He says that this reaction, appearing two or more hours after puncture, could not be due to intracranial hypotension, since the pressure of the cerebrospinal fluid following the removal of even large amounts of fluid returned to its original level within one or two hours and then mounted. Furthermore, postpuncture headache almost invariably occurred when the development of subarachnoid hypotension was prevented by the immediate reinjection of the fluid removed. It is therefore highly probable that the symptoms are due not only to a simple mechanical alteration in the subarachnoid hydrostatics but also to the congestion and edema of the central nervous system resulting from severe disturbances in its fluid balance. Leakage through the puncture wound in the dura plays little if any part in the causation of headache, according to Masserman. He

58. Brown, H., and Kolmer, J. A.: Sodium Formaldehyde Sulfoxylate in Experimental Acute Mercury Poisoning, J. Pharmacol. & Exper. Therap. **52**:462, 1934.

59. Dennie, C. C., and McBride, W. L.: Treatment of Resistant Somatic Syphilis, Arch. Dermat. & Syph. **30**:1 (July) 1934.

60. Masserman, J. H.: Intracranial Hydrodynamics: III. Central Nervous System Shock and Edema Following Rapid Fluid Decompression of Ventriculo-Subarachnoid Spaces, J. Nerv. & Ment. Dis. **80**:138, 1934.

is of the opinion that headache may be minimized by withdrawing the spinal fluid very slowly and that if it does develop it is best treated by measures calculated to relieve the shock and edema of the central nervous system (i. e., rest and the intravenous administration of dextrose, 250 cc. of a 20 per cent solution). The article is also valuable for a bibliography of 109 references.

Other Complications of Lumbar Puncture.—Reynolds and Wilson [61] report 3 interesting cases in which diagnostic lumbar puncture (the cerebrospinal fluid was normal in 2 cases and the condition was not mentioned in the third case) was followed in from six to twelve hours by headache, stiffness of the neck, stupor, delirium and fever. Repeated examination of the spinal fluid revealed sterile, cloudy fluid, with cell counts of 2,900, 3,780, and 17,670, respectively (from 85 to 95 per cent of the cells were polymorphonuclears), and there was prompt spontaneous recovery.

Among the little stressed complications of lumbar puncture is injury to the vertebrae. The report by Pease [62] is of special interest to me because of my experience with a patient in whom severe and disabling osteomyelitis of the third lumbar vertebra developed following lumbar puncture. Pease, prompted by the complaint of pain in the lower part of the back in many patients after lumbar puncture, observed in 12 cases thinning of the intervertebral disks and definite sclerosis of the vertebral bodies. This untoward result may occur if the needle is introduced too far and penetrates the intervertebral disk.

The Blood Spinal Fluid Barrier.—Masserman,[63] utilizing sodium bromide in 28 patients with dementia paralytica, confirms the results of Malamud and others that the permeability of the blood-spinal fluid barrier in this disease is significantly lower than in schizophrenic and in normal persons. The significance of these observations is not clear, either as to the etiology of neurosyphilis associated with dementia paralytica or as to its treatment, since in successfully treated patients it has been shown that the permeability of the barrier increases to or above normal. Considering the inefficacy of chemotherapeutic treatment (except with tryparsamide) in dementia paralytica, these results are the reverse of what would be expected.

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61. Reynolds, K. E., and Wilson, G.: Aseptic Meningitis Following Diagnostic Lumbar Puncture, J. A. M. A. **102**:1460 (May 5) 1934.

62. Pease, C. N.: Injuries to Vertebrae and Intervertebral Disks Following Lumbar Puncture, Am. J. Dis. Child. **49**:849 (April) 1935.

63. Masserman, J. H.: Blood-Cerebrospinal Fluid Barrier, with Especial Reference to Changes in General Paralysis and in Dementia Praecox, Psychiatric Quart. **9**:48, 1935.

TREATMENT IN EARLY SYPHILIS

The most important study of recent years dealing with the results of treatment of early syphilis is that of the Cooperative Clinical Group.[64] Five large clinics for syphilitic patients (the universities of Pennsylvania, Michigan, Western Reserve and Johns Hopkins and the Mayo Clinic) pooled their material and with the aid of the United States Public Health Service subjected it to critical statistical analysis. The detailed reports were published in *Venereal Disease Information* during 1931 and 1932. More readable summaries which omit the statistical details are provided in later important papers. The following summary is in part a direct quotation:[65]

> The maximum frequency of relapse in early syphilis under observation and treatment 6 months or longer is 19.7%. . . . The incidence of mucocutaneous relapse is lowest in those patients who have had a full secondary reaction to the disease. Patients who begin treatment in the seropositive primary stage have the highest incidence of mucocutaneous relapse. Nonetheless, no advantage appears on other grounds in permitting a seropositive primary case to go on to secondaries. The seropositive primary case must be treated with exceptional thoroughness. Relapse decreases in frequency with an increasing number of arsphenamine injections except in the case of cardiovascular and asymptomatic neurosyphilis. Satisfactory ("curative") treatment results are obtained in cases observed 2 years or longer (up to 20 years) in 52.7% of cases without respect to amounts and methods of treatment. Treatment begun in seronegative primary syphilis by a "continuous" system yields 86.4% "satisfactory results." The proportion of "satisfactory results" drops to 64.3% by the same method if the treatment is delayed until the serologic tests become positive. If the patient has developed secondaries, the proportion of "satisfactory results" (2 years and after) again rises to 81.5 % by a continuous system of treatment.

The authors state that the continuous method of treatment far outranks other systems (intermittent, intensive and irregular) in the proportion of ultimately satisfactory clinical outcomes. However, disregarding the system of treatment used, the optimum amount of arsphenamine was found to be: for seronegative primary syphilis, from 10 to 19 injections (preferably the higher number); for seropositive primary syphilis, from 25 to 35, and for early secondary syphilis (first year), from 20 to 29. A high scale of dosage is preferable to a low one. Ars-

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64. Stokes, J. H.; Cole, H. N.; Moore, J. E.; O'Leary, P. A.; Wile, U. J.; Parran, T., Jr.; Vonderlehr, R. A., and Usilton, L. J.: Standard Treatment Procedure in Early Syphilis: A Résumé of Modern Principles, J. A. M. A. **102**: 1267 (April 21) 1934.

65. Stokes, J. H.; Usilton, L. J.; Cole, H. N.; Moore, J. E.; O'Leary, P. A.; Wile, U. J.; Parran, T., Jr., and McMullen, J.: What Treatment in Early Syphilis Accomplishes: I. Relapse and "Curative" Results, Am. J. M. Sc. **188**: 660, 1934; II. Optimum Treatment. ibid. **188**:669, 1934; III. Comparison of Bruusgaard's Work and the Three- to Twenty-Year Results of the Coöperative Clinical Group, ibid. **188**:678, 1934.

phenamine is definitely superior to neoarsphenamine. In deciding when to stop treatment in the ordinary case, an uneventful clinical and serologic course toward recovery is paramount. In such an uneventful course the parole of the patient to observation after two years of adequate treatment is justified. The irreducible margin of failure in the treatment of early syphilis—the proportion of patients not likely to achieve or maintain a satisfactory result with any type of treatment—ranges from 4 to 29 per cent, depending on the method employed, the stage at which treatment is begun, the adequacy of treatment during the first two years of the infection and other considerations discussed in previous papers.

In comparing the results in the treated Cooperative Clinical Group patients with Bruusgaard's results in untreated patients, it was found that clinical evidence of neurosyphilis developed from two to four times as frequently in untreated as in treated patients and that late cutaneous and osseous lesions are from seventeen to twenty-six times as frequent in untreated patients. From 63 to 77 per cent of treated patients became free from symptoms and gave a negative Wassermann reaction in an observation period of from three to twenty years, as compared with from 24 to 36 per cent without treatment. After adequate treatment by an effective technic 96 per cent of patients became free from symptoms, with positive or negative reactions of the blood, after from three to ten years, while when no treatment was given only 61 per cent became symptom-free. While the relative benignity of many aspects of untreated syphilis is conceded, the results fully justify adequate and systematic modern treatment for early syphilis.

Massive Arsenical Treatment of Early Syphilis.—Chargin, Leifer and Hyman [66] have restudied the effect of massive doses of arsphenamine on early syphilis. They report on 25 patients, each of whom was given a total dose of from 2.4 to 5 Gm. of neoarsphenamine in from four to six days, the average daily dose being 1 Gm. No further treatment was given. The original feature of the method was the administration of the drug by slow intravenous drip, each daily injection being given in from approximately 1,000 to 1,500 cc. of a 5 per cent solution of dextrose over a period of from six to twelve hours. The theory was to reduce toxicity and to provide a massive sterilizing dose of the drug. The former aim was hardly accomplished, since in eight patients (32 per cent) polyneuritis developed and was severe in 2 instances. However, no other serious complications occurred. Nine of the 25 patients

66. Chargin, L.; Leifer, W., and Hyman, H. T.: Studies of Velocity and the Response to Intravenous Injections: V. The Application of the Intravenous Drip Method to Chemotherapy, as Illustrated by Massive Doses of Arsphenamine in the Treatment of Early Syphilis, J. A. M. A. **104**:878 (March 16) 1935.

were followed for more than sixteen weeks (for total periods ranging from six to twelve months). In all these the serologic reactions became negative, and no clinical relapses were observed.

I am less enthusiastic than the authors about the adoption of this method on a large scale because of (1) the high incidence of polyneuritis as a complication of treatment; (2) the almost invariable early or late clinical relapses observed after large single (or multiple) doses of arsphenamine given in the first few years after its introduction in 1909 and 1910; (3) the comparatively complete inefficacy on all counts of the intensive (Pollitzer) system of treatment, as shown by the careful studies of the Cooperative Clinical Group; (4) the inadequate period of observation of the patients so far treated; (5) the lack of demonstration that the intravenous drip method of administering 1 Gm. of, for example, arsphenamine is superior in therapeutic effect to the administration of the same amount in a small volume of fluid and in a short period of time, and (6) the absence of evidence of the harmlessness of this method of treatment in experimental animals.

GLANDULAR TRANSFER AS EVIDENCE OF CURE OF SYPHILIS

Lunsford and Day [67] have performed the largest recorded series of inoculations of rabbits with the inguinal glands of untreated and treated syphilitic patients. Infection was transmitted to animals successfully with material from the following patients: 8 patients with untreated primary syphilis, 100 per cent; 29 patients with late syphilis, no previous treatment, 38 per cent; 38 patients with late syphilis, previously treated but not for two years, 31.5 per cent; 19 patients with late syphilis under active treatment at the time of the test, none; 6 patients with dementia paralytica, no previous treatment, none. The authors lay great stress on the fact that in 3 of the patients previously treated intensively treatment had been started at the time of primary or secondary syphilis and had consisted of from forty-one to one hundred and twenty-eight injections of neoarsphenamine plus appropriate amounts of a bismuth and/or mercury preparation. These patients had been dismissed as "cured" on the basis of negative serologic tests, but glandular transfer was nevertheless effected from three to five years later. However, since the Wassermann reaction of the blood in all these patients was positive at the time of the transfer and since nothing is said about clinical evidences of reinfection or relapse, the case reports are robbed of much of their meaning. The conclusion to be drawn from these experiments is that glandular transfer from human beings to animals is of no value as a criterion of cure (as is transfer from rabbit to rabbit), since

67. Lunsford, C. J., and Day, P. W.: Transference of Inguinal Glands in Human Syphilis, J. A. M. A. **102**:448 (Feb. 10) 1934.

the test gives negative results in such a high proportion of patients with previously untreated and active late syphilis.

TREATMENT OF BENIGN LATE SYPHILIS

Adding to the completeness of studies of the results of treatment of various types of syphilitic infection, Wasserman and Goodman [68] recount the clinical outcome of treatment in 250 patients with benign late (i. e., mucocutaneous and osseous) syphilis. Their important conclusions are as follows: The outcome of treatment must be measured in clinical rather than serologic terms; a persistently positive Wassermann reaction in a case of benign late syphilis does not imply a gloomy clinical prognosis, nor does reversal of the reaction guarantee against subsequent clinical relapse; the incidence of clinical relapse is directly related to the amount of treatment given (31 per cent with one course of treatment or less, 5 per cent with four courses or more); the character of the relapse is particularly likely to be of the same allergic gummatous type as the original lesion, and the optimum amount of treatment in such cases appears to be from five to seven courses each of an arsphenamine and a heavy metal given continuously over an average period of from eighteen to twenty-four months.

LATENT SYPHILIS

Carriers of Syphilis.—The question as to the potential infectiousness of a patient with late syphilis is of great importance, both from the personal and from the public health standpoint. Since Eberson and Engman reported in 1921 that in 2 of 11 men with late syphilis the semen was infectious for rabbits, the subject has not received the attention it deserves. Kertész has stated in recent years that by means of inoculation of semen into the vitreous of the eye of rabbits he is able to produce what he calls syphilitic keratitis with a high degree of frequency. Unfortunately, proof that this keratitis is syphilitic is completely lacking. The paper by Greenbaum, Katz and Rule [69] is therefore particularly timely. They inoculated rabbits intratesticularly with the semen of 7 patients with "acute" (early?) syphilis, of 17 with various forms of late or latent syphilis and of 1 with congenital syphilis. All the inoculations gave negative results, as confirmed by transplants of lymph nodes from the original animals to fresh rabbits. Unfortunately,

68. Wasserman, H., and Goodman, M. J.: The Results of Treatment in Late Mucocutaneous and Osseous (Benign Late) Syphilis, Am. J. Syph. & Neurol. **18**:458, 1934

69. Greenbaum, S.; Katz, S., and Rule, A.: Syphilis and Marriage: An Inquiry into the Infectiousness of Semen of Patients Under Treatment for Syphilis, Am. J. Syph. & Neurol. **19**:210, 1935.

the study is less important than it might have been, since all the patients had been under energetic treatment for syphilis for some weeks or months preceding the test. What is really needed are similar experiments utilizing patients who have never had treatment or at least have not been treated for several years preceding the test.

Blood Transfusion and Syphilis.—This subject has recently been reviewed, and cases have been added by Jones, Rathmell and Wagner [70] (4 personal cases) and by Morgan [71] (1 case). The most remarkable feature of these two communications is that in spite of the known frequency of this disastrous occurrence (I have definite knowledge of 7 instances) a thorough review of the literature reveals the reports of only about 20 recorded cases. In the majority of reported instances the donor had an early stage of the disease. Not a single incontestable case of syphilis due to blood transfusion has been reported in which the disease was transmitted by blood from a donor with latent or chronic syphilis uninfluenced by pregnancy (Morgan's statement, though I have recently observed such a case).

On the whole, it seems safer to agree with Jones, Rathmell and Wagner, who conclude that all syphilitic patients are potential transmitters, and to throw the most rigid safeguards around the procedure of transfusion. These should include (1) a written, not verbal, report of a serologic test of the donor's blood carried out on the day that the transfusion is to be given, (2) physical examination of the donor and (3) the resort to an "emergency" transfusion without these precautions only when immediate action is demanded in order to save a life.

CONGENITAL SYPHILIS

Syphilis and Pregnancy.—The outcome of 943 pregnancies in syphilitic women is reported by McKelvey and Turner [72] in a paper which constitutes the most important contribution to this subject that has been made in several years. Detailed data are presented to aid in the evaluation of the Wassermann reaction of blood from the cord (which the authors believe to be of distinct though not of definitive value), of the histologic characteristics of the placenta, of roentgenograms of an infant's long bones and of the results of a follow-up study and pediatric study in determining the presence or absence of syphilis in an infant. It is clearly shown that with adequate treatment (the results being pro-

70. Jones, H. W.; Rathmell, T. K., and Wagner, C.: The Transmission of Syphilis by Blood Transfusion, Am. J. Syph. & Neurol. **19**:30, 1935.

71. Morgan, H. J.: Factors Conditioning the Transmission of Syphilis by Blood Transfusion, Am. J. M. Sc. **189**:808, 1935.

72. McKelvey, J. L., and Turner, T. B.: Syphilis and Pregnancy, J. A. M. A. **102**:503 (Feb. 17) 1934.

portional to the amount of treatment given and the time at which it is begun) congenital syphilis may be prevented (or if established, successfully treated in utero) with almost absolute certainty.

The survey of the Cooperative Clinical Group [73] on this same subject gives a review of the outcome of 607 pregnancies in syphilitic women. The conclusions are practically identical with those of McKelvey and Turner.

McCord's latest paper [74] gives the reports of 2,500 additional well studied cases. The outcome of pregnancy with varying amounts of antisyphilitic treatment and the effect of treatment on such factors as the Wassermann reaction of blood from the cord and necropsy and roentgenologic observations on dead infants are presented in a series of illuminating tables.

Eastman and Dippel [75] have made an important contribution to the solution of the question: Does treatment of the syphilitic pregnant woman prevent infection of the fetus, or may it also treat a fetus with an already established infection? Although they were unable to demonstrate arsenic in the fetal blood following treatment of the mother with arsphenamine, it was observed in substantial concentration in the meconium. This suggests that whatever the manner (probably not simple diffusion through the placenta) in which arsenic is transmitted from mother to fetus, arsenic is metabolized by the fetus in the usual manner and is available for the treatment of an already established fetal infection.

Experimental Fetal Syphilis.—Attempts to solve experimentally some of the problems of the transmission of syphilis from mother to fetus have been made by Levaditi and his associates,[76] Nyka [77] and

73. Cole, H. N., and others: Syphilis in Pregnancy, Ven. Dis. Inform. **15**:83, 1934.

74. McCord, J. R.: Syphilis and Pregnancy: A Clinical Study of 2,150 Cases, J. A. M. A. **105**:89 (July 13) 1935.

75. Eastman, N. J., and Dippel, A. L.: The Passage of Arsenic Through the Human Placenta Following Arsphenamine Therapy, Bull. Johns Hopkins Hosp. **53**:228, 1933.

76. Levaditi, C.; Hornus, G.; Vaisman, A., and Schoen, R.: Présence du virus syphilitique dans l'ovaire des souris syphilisées par voie sous-cutanée, Compt. rend. Acad. d. sc. **197**:798, 1933. Levaditi, C.; Schoen, R.; Manin, Y., and Vaisman, A.: Présence de T. pallidum dans l'uterus des souris contaminées de syphilis, Compt. rend. Soc. de biol. **114**:687, 1933; Présence de T. pallidum dans l'ovaire des souris contaminées de syphilis, Compt. rend. Acad. d. sc. **197**:1364, 1933; Infection treponémique utéro-ovarienne et cycle oestral folliculinique chez la souris blanche, Compt. rend. Soc. de biol. **116**:376, 1934. Levaditi, C.; Vaisman, A.; Schoen, R., and Manin, Y.: Tentatives de transmission héréditaire de l'infection syphilitique inapparente chez la souris blanche, ibid. **118**:962, 1935.

77. Nyka, W.: Contribution á l'étude du mécanisme de la transmission de la syphilis de la mère à l'embryon chez la lapine et la souris, Compt. rend. Soc. de biol. **114**:1258, 1933.

Seiffert.[78] Though the uterus and ovaries of the syphilitic white mouse can be shown (by transfer of organs from a rabbit) regularly to contain virulent spirochetes, this has no apparent effect on the fecundity or on the fetal mortality. In the mouse the placenta seems to be impermeable to the virus, and the young are never infected (Levaditi and his associates). Seiffert confirms this statement as to the mouse, but in rabbits he has apparently demonstrated the virus in some instances in the placenta and, if the placenta was infected, in the young as well. Nyka has tried the artificial experiment of directly inoculating the ovaries of rabbits, breeding them subsequently. He also expresses the belief that following this procedure the fetus may become infected and that, depending on the duration of pregnancy, either "filamentous" or spiral forms of the virus can be demonstrated in the fetal tissues.

While the results of these three studies are inconclusive, this type of investigation merits further pursuit, since the experimental approach is the only one likely to be productive of a solution.

Interstitial Keratitis.—In a paper well supplied with bibliographic references Klauder [79] discusses the relationship of trauma to interstitial keratitis in syphilis. A general discussion of the relationship of trauma to the localization of syphilitic lesions in man and experimental animals is provided. Occasionally, trauma precedes the development of interstitial keratitis in man, and workmen's compensation boards have usually favored the plaintiff in this connection. Experimental studies in rabbits were inconclusive.

Ambler and Van Cleve [80] report the results of malarial therapy in 17 patients with interstitial keratitis, in 10 of whom previous chemotherapy had been unsatisfactory. The results were excellent in all, even in the most chronic cases.[81] The authors express the belief that malarial treatment possesses distinct advantages over any other known method of treatment for interstitial keratitis.

Treatment of Interstitial Keratitis with Quinine.—In view of the poor results of antisyphilitic treatment in some cases of interstitial keratitis, Selinger [82] was moved to try the local application of 2 per cent

78. Seiffert, W.: Experimentelle Untersuchungen über die Infektion mit S. pallida durch Kohabitation und durch die Plazenta, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:386, 1934.

79. Klauder, J. V.: Ocular Syphilis: IV. Interstitial Keratitis and Trauma; Clinical, Experimental and Medicolegal Aspects, Arch. Ophth. **10**:302 (Sept.) 1933.

80. Ambler, J. V., and Van Cleve, J. V.: Malarial Therapy in Syphilitic Interstitial Keratitis, J. A. M. A. **102**:1553 (May 12) 1934.

81. See also Dennie and McBride.[59]

82. Selinger, E.: Local Quinine Therapy in Cases of Interstitial Keratitis and Old Corneal Opacities, Arch. Ophth **13**:829 (May) 1935.

quinine bisulphate ointment. Quinine, he says, not only is bactericidal and astringent but destroys leukocytes and lymphocytes and probably aids in the resorption of abnormal tissue elements, such as newly formed connective tissue in the cornea. He used this treatment on several patients with active interstitial keratitis and on several others without active keratitis but with dense corneal opacities and claims that some improvement was obtained in all.

Articular Changes in Late Congenital Syphilis.—Klauder and Robertson [83] review the literature and describe the cases of 63 personally observed congenitally syphilitic patients with symmetrical serous synovitis (Clutton's joints). This is a manifestation of late congenital syphilis, usually involving the knees. The authors describe the clinical course, the age incidence (usually between 8 and 15 years), the absence of changes that are demonstrable in roentgenograms, the pathology, the differential diagnosis, the response to treatment, the incidence as compared to other stigmas of congenital syphilis (17 per cent of 363 patients in their series had Clutton's joints) and the peculiar tendency of this lesion to be associated with interstitial keratitis.

Juvenile Dementia Paralytica.—In a series of twelve interesting, important and well documented articles, eleven of which have appeared, Menninger [84] reviews in monographic form the entire subject of juvenile dementia paralytica. His conclusions are based on 45 personally observed patients and on 610 cases reported in the literature. The more important of his conclusions that have been published are as follows: In about 1 per cent of all patients with congenital syphilis, juvenile dementia paralytica develops, a lower incidence than in patients with the acquired disease. While dementia paralytica in the acquired form is nearly three and one-half times as frequent in men as in women, the juvenile form has an almost equal incidence in boys and in girls.

83. Klauder, J. V., and Robertson, H. F.: Symmetrical Serous Synovitis (Clutton's Joints), J. A. M. A. **103**:236 (July 28) 1934.

84. Menninger, W. C: Juvenile Dementia Paralytica: I. Incidence, Sex and Age of Onset, Am. J. Syph. & Neurol. **18**:486, 1934; II. Family History, Arch. Int. Med. **55**:626 (April) 1935; III. Developmental History, Including Mental and Physical Growth, Trauma and Convulsions, J. Nerv. & Ment. Dis. **81**:489 (May) 1935; IV. Syndrome of the Cranial Nerves and Motor System, Arch. Neurol. & Psychiat. **34**:243 (Aug.) 1935; V. Sensory Changes and the Reflexes in Juvenile Paretic Neurosyphilis, Ann. Int. Med. **8**:1287 (April) 1935; VI. Physical Complications, Stigmas, and Endocrinopathies, Am. J. Syph. & Neurol. **19**:88, 1935; VII. The Descriptive Mental Picture, Am. J. Psychiat., **91**:1413 (May) 1935; VIII. The Psychology of Juvenile Dementia Paralytica, Psychoanalyt. Rev., to be published; IX. Laboratory Findings, J. Lab. & Clin. Med. **20**:806 (May) 1935; X. The Clinical Course, Including Prodromal Symptoms, Nature of Onset, Remissions, and Duration, Am. J. Syph. & Neurol. **19**:238, 1935; XI. Treatment, ibid. **19**:257, 1935; XII. Gross and Microscopic Pathology, Arch. Path. **19**:316 (March) 1935.

The average age at onset is 13 years. Few cases occur before the sixth or after the twentieth year of life. Four times as many mothers of patients with juvenile dementia paralytica have neurosyphilis as unselected syphilitic women, and nearly twice as many fathers have neurosyphilis as average syphilitic men. In both parents the type of neurosyphilis, when present, is predominantly that of dementia paralytica. In the siblings of persons who have had juvenile dementia paralytica, neurosyphilis is likewise common. These facts may be accepted equally well as arguments for a neurotropic strain of virus as for a familial predisposition.

Menninger found that 40 per cent of patients with juvenile dementia paralytica were definitely retarded mentally before the onset of symptoms. The type of preceding feeblemindedness differed in no way from other types of mental deficiency, but Menninger believes it is an indication of syphilis of the brain. In 35 per cent of all his cases, physical development likewise was retarded. This retardation is primarily an arrest of growth and results in a type of infantilism.

Trauma preceded the onset of symptoms in dementia paralytica in 35 of 349 patients. Convulsions, usually typical of the idiopathic grand mal of epilepsy, occurred at some time, often prior to the development of any other symptom, in 17 per cent of the entire series (31 per cent of those in whom adequate data were provided).

The article on treatment is especially well documented, containing 375 references. The results of treatment are disappointing as compared with those for acquired syphilis. Of 144 cases adequately reported, marked improvement occurred in 13.8 per cent, slight improvement in 25.1 per cent and no effect in 61.1 per cent. The therapeutic agents employed included malaria, diathermy, arsphenamine and tryparsamide. The following factors condition the outcome of treatment: Patients who acquire the disease after a period of normal growth respond better than basically feebleminded subjects; the onset of symptoms during or after puberty offers a better prognosis than an onset prior to that time; the outlook is better the sooner treatment is inaugurated after the onset of symptoms of dementia paralytica; the influence of previous antisyphilitic treatment, of the sex of the patient and of the type of the psychosis does not seem to play any prognostic rôle; malaria, diathermy and tryparsamide have all given better results than the arsphenamines; treatment must be intensive, prolonged and continuous, i. e., without rest periods.

The pathologic picture of juvenile dementia paralytica, while similar in most respects to that in the adult form, shows certain differences. The characteristic macroscopic changes are generalized atrophy, often hypoplastic, of the brain; marked leptomeningitis; frequently hydro-

cephalus, and extensive ependymitis granulosa. In rare cases gummas of the brain may be present. Microscopically, there are generalized round cell infiltration, extensive neuroglial and microglial proliferation, an increase in vascularity with proliferative changes in all the elements of the vessel walls, a reduction of the number of nerve cells in the cortex and binucleated Purkinje cells in the cerebellum. Spirochetes have been demonstrated in the cortex, the basal ganglions and the cerebellum.

Potter [85] reports the results of treatment in 60 personally observed patients with juvenile dementia paralytica. The arsphenamines were useless. In 27 of 38 patients (the surprisingly high figure of 71 per cent) treated with malaria, tryparsamide or both, further deterioration was prevented. Five patients achieved a complete, and 9 a partial, remission. The period of observation was in most cases from two to five years. The factors influencing prognosis, according to Potter, are essentially those enumerated by Menninger.

The communications of both of these authors are important in pointing out that the malaria-tryparsamide treatment of juvenile dementia paralytica is by no means hopeless and that patients should be given the benefit of a trial.

Use of Acetarsone in Congenital Syphilis.—During the past three years numerous investigators, especially in Germany and in the United States, have studied the effect of acetarsone in congenital syphilis. In most instances the reports have been more glowingly favorable than was warranted by the small number of patients treated and the short period of observation. Pillsbury and Perlman [86] undertook a study of 73 patients. With commendable caution they conclude that, while the clinical response seemed excellent and the initial serologic response was satisfactory, the method is to be regarded as on trial. They point out that the dosage level is still in dispute, that the desirability of combined therapy with some type of heavy metal has not been determined, that serious reactions are sometimes produced by the drug and that a follow-up of the treated patients for a period of from five to ten years will be essential for a proper evaluation of the method.

Friedman [87] reports favorably on the use of acetarsone in 5 infants with osseous lesions of congenital syphilis. Baumbach,[88] with an experi-

85. Potter, H. W.: Treatment of Juvenile General Paresis, Psychiatric Quart. **7**:593, 1933.

86. Pillsbury, D. M., and Perlman, H. H.: Treatment of Prenatal Syphilis with Acetarsone (Stovarsol), Pennsylvania M. J. **38**:327, 1935.

87. Friedman, C. F.: Acetarsone in the Treatment of Osseous Lesions of Early Congenital Syphilis, Am. J. Dis. Child. **48**:548 (Sept.) 1934.

88. Baumbach: Ueber Erfahrungen mit der Spirocidkur bei Lues Congenita, Arch. f. Kinderh. **99**:151, 1933.

ence covering 61 cases, concludes that the best results are obtained when acetarsone is alternated with mercury by inunction. Traisman [89] has also achieved favorable results in 54 patients. Yampolsky,[90] on the basis of his experience with 16 children, is disposed to be more cautious. Coppolino [91] and Eckardt [92] also report on this method of treatment.

In reporting two cases (one fatal) of myelitis and peripheral neuritis following the use of acetarsone in infants, Glaser [93] sounds a timely note of warning that caution is necessary.

GASTRIC SYPHILIS

The perennial argument of therapeutic test versus exploratory laparotomy in patients with suspected gastric syphilis is somewhat clarified by Priestley and Walters.[94] They point out that a delay of several weeks for a therapeutic test is undesirable if there is any possibility that a lesion is malignant. Cases in which medical treatment is justified from the start are (1) those in which the diagnosis of gastric syphilis is practically certain before a therapeutic test is made (a rare circumstance in my opinion) and (2) those in which the gastric lesion is obviously inoperable, whether as a result of syphilis or of a malignant process. Operation before a therapeutic test is made should be carried out (1) in patients with serologic evidence of syphilis and an operable malignant gastric tumor or a nonspecific inflammatory gastric lesion requiring intervention because of obstruction or perforation and (2) in patients with serologic evidence of syphilis associated with a definite gastric lesion the clinical diagnosis of which is indeterminate between malignancy and syphilis (in my personal experience most cases of suspected gastric syphilis fall into one of the two latter categories). With commendable caution the authors call attention to the difficulty of recognizing gastric syphilis even at exploration and suggest that if there is any doubt in the mind of the operator, resection, if feasible, should be performed.

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89. Traisman, A. S.: Treatment of Congenital Syphilis with Acetarsone (Stovarsol) by Mouth, Am. J. Dis. Child. **46**:1027 (Nov.) 1933.

90. Yampolsky, J.: Acetarsone in the Treatment of Syphilis in Negro Children, Am. J. Dis. Child. **48**:81 (July) 1934.

91. Coppolino, J. F.: Acetarsone in the Treatment of Congenital Syphilis: A Comparison with Bismuth Therapy, Am. J. Dis. Child. **48**:272 (Aug) 1934.

92. Eckardt, F.: Spirozid bei Lues Congenita (Zur Frage der Dosierung und Indikation sowie Ergebnisse), Jahrb. f. Kinderh. **141**:278, 1934.

93. Glaser, J.: Clinical Arsenical Myelitis and Neuritis Due to Acetarsone, Am. J. Dis. Child. **48**:134 (July) 1934.

94. Priestley, J. T., and Walters, W.: Indications for Operation in Gastric Syphilis, Surg., Gynec. & Obst. **58**:1030, 1934.

Pernicious Anemia Following Resection for Gastric Syphilis.—Singer and Steigman [95] add another to the 4 previously reported cases of pernicious anemia following partial or complete resection for gastric syphilis. Their article is particularly valuable for a summary and bibliography of 33 other instances in which primary anemia followed total or subtotal gastrectomy or gastro-enterostomy for carcinoma, ulcer or some other condition.

CARDIOVASCULAR SYPHILIS

A reawakening of interest in the subject of cardiovascular syphilis has been evident within the past few years, prompted in all probability by the demonstrations that the early diagnosis of uncomplicated syphilitic aortitis is possible with accuracy in many instances before the development of saccular aneurysm or aortic regurgitation and that properly directed treatment is often successful in alleviating symptoms and prolonging life. In the Billings lecture Conner [96] provides a timely and valuable discussion of the development of knowledge in the general field of cardiovascular syphilis. Lisa and Chandlee [97] utilize 6 cases as the basis of their discussion of the comparatively frequent association of syphilitic and rheumatic cardiac disease and point out that the combined active infections carry a much graver prognosis than that of either infection when it occurs alone.

Maynard and his associates [98] report a careful study of the cardiovascular status of 346 patients with syphilis. They have made an effort to study the life history of syphilitic patients with cardiovascular involvement starting with the chancre and ending at necropsy. In this sense their paper is a preliminary communication, since most of their patients are still living. They join with earlier observers in stating that they feel that the diagnosis of uncomplicated syphilitic aortitis is possible with a high degree of accuracy. Their material is particularly noteworthy for the unusually high incidence of cardiovascular syphilis discovered at routine examination. The patients were divided into five groups, depending on the interval between the date of infection and the time of the cardiovascular study, as follows: up to three, from four to nine, from ten to nineteen, from twenty to twenty-nine and for thirty or more years. The

95. Singer, H. A., and Steigman, F.: Pernicious Anemia Following Resection for Gastric Syphilis, Am. J. Syph. & Neurol. **18**:444, 1934.

96. Conner, L. A.: Development of Knowledge Concerning the Rôle of Syphilis in Cardiovascular Disease, J. A. M. A. **102**:575 (Feb. 24) 1934.

97. Lisa, J. R., and Chandlee, G. J.: The Heart and Great Vessels in Combined Syphilitic and Rheumatic Infection, Arch. Int. Med. **54**:952 (Dec.) 1934.

98. Maynard, E. P., Jr.; Curran, J. A.; Rosen, I. T.; Williamson, C. G., and Lingg, C.: Cardiovascular Syphilis: Early Diagnosis and Clinical Course of Aortitis in Three Hundred and Forty-Six Cases of Syphilis, Arch. Int. Med. **55**:873 (June) 1935.

incidence of detectable cardiovascular syphilis in these five groups increased progressively as follows: 14, 28, 56, 77 and 88 per cent, respectively. Unfortunately, the authors do not give the exact figures for the number of patients in each group with simple aortitis, aortic regurgitation and saccular aneurysm, respectively. Since the patients were predominantly white (81 per cent) and since these figures as to the incidence of clinically (*not* pathologically) recognizable cardiovascular syphilis are so vastly in excess of those reported by other observers the world over, one wonders if some unconscious selection did not enter into the choice of material. Also contrary to the experience of others, the authors conclude that cardiac failure occurs only in those patients in whom syphilitic involvement has passed beyond the stage of simple aortitis to the development of valvular incompetency, aneurysm or narrowing of the coronary arteries. Their final conclusion is, however, of the utmost importance and deserves special emphasis:

> It is our opinion that involvement of the aorta begins soon after the chancre has appeared and that in the past, discovery of the presence of the disease has been delayed by the late development of symptoms referable to the heart and more especially by inadequate methods of examination.

The moral for the physician who treats syphilitic patients is clear.

Syphilitic Involvement of the Coronary Arteries.—Van Muijden and Scherf [99] divide angina pectoris into 6 categories, which they say can easily be differentiated, occurring (1) in coronary thrombosis or infarct, (2) in coronary stenosis (angina of effort), (3) in aortic insufficiency (usually nocturnal and accompanied by an increase in the blood pressure), (4) in paroxysmal tachycardia, (5) in anemia and (6) in syphilitic involvement of the coronary ostia. In cases belonging in the sixth category anginal attacks may develop with or without exertion, and anxiety attacks without pain may occur. During an attack there is tachycardia but no elevation of the blood pressure, and nitrites provide relief. The prognosis is unfavorable. Snider and Hunter [100] describe the necropsy observations in such a case.

On the basis of 15 patients studied clinically and at necropsy, Pincoffs and Love [101] conclude that syphilitic stenosis of the coronary ostia

99. van Muijden, N. H., and Scherf, D.: Ueber ein durch hochgradige luische Verengerung der Coronarostien hervorgerufenes Krankheitsbild, Wien. klin. Wchnschr. **47**:746, 1934.

100. Snider, G. A. C., and Hunter, W. C.: Syphilitic Aneurysm of the Left Coronary Artery with Concurrent Aneurysm of the Sinus of Valsalva, Am. J. Path. **10**:757, 1934.

101. Pincoffs, M. C., and Love, W. S.: Observations upon Syphilis of the Heart, Coronary Ostia, and Coronary Arteries: I. With Special Reference to Clinical Picture Produced by Syphilitic Stenosis of Coronary Ostia, Am. J. Syph. & Neurol. **18**:145, 1934; II. With Special Reference to the Myocardial Lesions Noted in Stenosis of the Coronary Ostia, ibid. **18**:154, 1934.

is a very common lesion. It is rarely latent; the clinical course after the onset of symptoms is usually brief and characterized by a lack of response to treatment, a high incidence of the occurrence of anginal pain and a marked tendency to terminate by sudden death. The coincidence of these factors in a patient with cardiovascular syphilis constitutes a clinical picture recognizable as syphilitic occlusion of the coronary ostia. The myocardial lesions present in such cases are explainable on the basis of a defective coronary circulation due to obliterative endarteritis of the coronary arterioles. No pathologic evidence justifying a diagnosis of syphilitic myocarditis could be demonstrated.

Thyroidectomy as a Method of Treatment for Advanced Syphilitic Cardiac Disease.—In the brilliant series of studies of Blumgart, Levine and their associates [102] on the treatment of advanced cardiac decompensation and angina pectoris by total thyroidectomy, syphilitic cardiac disease has been purposely almost completely excluded on the ground that the lesion in such instances is almost surely progressive and amenable only to temporary, if any, improvement. Since in the early phases of this condition this method of treatment was purely experimental, it was justifiable to limit its use to the most favorable type of cases. With the demonstration by Moore, Danglade and Reisinger,[103] among others, that symptoms may be alleviated and life prolonged by the properly controlled use of antisyphilitic treatment, trial of the method of thyroidectomy in selected cases of syphilitic cardiac disease seems desirable. Pratt [104] takes the same point of view and presents cases which suggest the favorable action of the procedure. Only patients for whom other therapeutic measures have failed are at present eligible for the operative procedure.

The Effect of Antisyphilitic Treatment in Prolonging Life in Cases of Cardiovascular Syphilis.—The contentions of Moore, Danglade and Reisinger [103] that properly conducted antisyphilitic treatment in cases of cardiovascular syphilis will materially prolong life have found some support in the monumental study of Grant [105] from the clinic of Sir Thomas Lewis. Included in this report are the cases of 189 patients with syphilitic aortic insufficiency who were followed until death or, if

102. Blumgart, H. L., and others: Total Ablation of Thyroid in Angina Pectoris and Congestive Failure: Summary of Results in Treating Seventy-Five Patients During Last Eighteen Months, J. A. M. A. **104**:17 (Jan. 5) 1935.

103. Moore, J. E.; Danglade, J. H., and Reisinger, J. E.: The Treatment of Cardiovascular Syphilis, Arch. Int. Med. **49**:879 (June) 1932.

104. Pratt, G. H.: Complete Thyroidectomy in Advanced Heart Disease, with Observations on Its Use in Advanced Arteriosclerosis, Syphilis, and Renal Disease, Am. J. Surg. **28**:85, 1935.

105. Grant, R. T.: After Histories for Ten Years of a Thousand Men Suffering from Heart Disease, Heart **16**:275, 1933

living, for a minimum period of ten years. Some of these patients had been allowed to go without antisyphilitic treatment, some had received potassium iodide only and some had been given neoarsphenamine, mercury (at intervals) and potassium iodide. The general medical care was the same for all the patients. There appeared to be no advantage in the use of potassium iodide alone, and the outcome in this and that in the untreated groups were so similar that they may be combined. During the period of observation the mortality rate from all causes in these two groups was 66 per cent, the deaths due directly to cardiovascular syphilis constituting 59 per cent. The corresponding figures for the treated patients were, on the contrary, 49 and 33 per cent, a very material reduction. Grant discusses many collateral factors affecting prognosis in this and other types of cardiac disease.

NEUROSYPHILIS

An interesting symposium on neurosyphilis is presented by Moore, Merritt and Solomon.[106] The subject of acute syphilitic meningitis is covered in monographic fashion in a later publication by Merritt and Moore,[107] on the basis of 80 patients studied by them in Boston hospitals. They provide a complete discussion of the incidence relation to treatment, clinical type, course, serology, pathology, prognosis and treatment, giving a fairly complete bibliography of 66 titles.

The most interesting features of the symposium are those relating to the results of treatment. The authors state that in cases of acute syphilitic meningitis there is a ready response to antisyphilitic drugs and that if treatment is prolonged the ultimate prognosis is good. In cases of dementia paralytica complete arrest and even cure may often be attained by appropriate treatment. Solomon's results with malaria were definitely superior to those obtained with diathermy.

Goodman and Moore [108] have studied the important practical question of the relationship of persistent abnormality of the spinal fluid to the ultimate clinical outcome in treated patients with neurosyphilis. If treatment was given for two or more years, subsequent progression or relapse occurred in 12.5 per cent of the patients who gave persistently positive Wassermann reactions of the spinal fluid as compared with 4.8 per cent

106. Symposium on Neurosyphilis: I. Moore, M.: Acute Syphilitic Meningitis, J. Nerv. & Ment. Dis. **80**:320, 1934. II. Merritt, H. H.: Syphilis of the Spinal Cord, ibid. **80**:322, 1934. III. Solomon, H. C.: Treatment of Paretic Neurosyphilis, ibid. **80**:323, 1934; IV. Solomon, H. C.: Recapitulation, ibid. **80**:324, 1934.

107. Merritt, H. H., and Moore, M.: Acute Syphilitic Meningitis, Medicine **14**:119, 1935.

108. Goodman, M. J., and Moore, J. E.: Persistent Abnormalities (Wassermann-Fastness) of the Spinal Fluid in Treated Neurosyphilis: Their Prognostic Import, Arch. Int. Med. **55**:826 (May) 1935.

of those whose reactions were reversed. They conclude that while there is a slightly more definite relationship between the clinical outcome and the response of the spinal fluid in neurosyphilis than exists between reversal and persistent positivity of the Wassermann reaction of the blood in various forms of late syphilis not involving the nervous system, nevertheless, a persistent abnormality of the cerebrospinal fluid does not indicate the inevitability of subsequent progression or relapse, and the rate or completeness of reversal of the abnormalities of the fluid cannot be used as the sole guide to the optimum duration of treatment in neurosyphilis. Dattner [109] has arrived at essentially similar conclusions.

Involvement of the Eighth Nerve.—Ciocco and Weinstein [110] have brought some clarity out of the confused subject of nerve deafness in syphilis, and their study is particularly important because it is the first report in which the audiometer has been used in a detailed study of the problem. Two hundred and eighty-six patients with syphilis were studied, special attention being given to the effects of treatment on hearing. All patients with infection of the middle ear or of deafness antedating the acquisition of syphilis were excluded. Shortened bone conduction in the presence of good hearing was not observed except when the capability of hearing high tones had been lost. Vestibular function was disturbed in half the patients with marked impairment of hearing but was diminished in about 33 per cent of the patients with normal hearing. Involvement of the eighth nerve in acquired syphilis, but not in congenital syphilis, was usually associated with neurosyphilis; but the authors state that a diagnosis of neurosyphilis based solely on an impaired function of the eighth nerve is not justified. There is no evidence that antisyphilitic treatment damages the eighth nerve. With the exception of deafness associated with early meningeal neurosyphilis, treatment is without effect in improving the hearing. The exact site of the lesion in nerve deafness, either in acquired or congenital syphilis, is unknown.

Subdural Treatment of Neurosyphilis.—Bonorino Udaondo and his associates [111] have experimented with the intraspinal injection of a bismuth compound (bismuth carbonate) in the treatment of various types of neurosyphilis. The drug was tolerated in a dosage of from 0.015 to 0.12 Gm. per injection without untoward results. They report that it is

109. Dattner, B.: Ueber die prognostiche Bedeutung der Wassermann-Reaktion bei Neurolues, Jahrb. f. Psychiat. u. Neurol. **48**:112, 1932.

110. Ciocco, A., and Weinstein, A.: Involvement of the Eighth Nerve in Syphilis with Special Reference to the Results of Treatment, Am. J. M. Sc. **187**:100, 1934.

111. Bonorino Udaondo, C.; Pereyra Kafer, J., and Zunino, H.: Intraspinal Bismuth Therapy, Prensa méd. argent. **22**:509, 1935.

as yet too early to measure the clinical improvement. However, there is no reason to believe that the intraspinal administration of bismuth will exercise any effect other than that produced by the subdural injection of other substances, and the weight of American opinion is that this effect is entirely nonspecific.

Treatment of Atrophy of the Optic Nerve.—The present unsatisfactory state of the treatment of primary atrophy of the optic nerve due to syphilis is exemplified by the three papers of Schiff-Wertheimer,[112] Gasteiger [113] and Magitot.[114] Schiff-Wertheimer believes that some patients are benefited and that arrest of the process is obtained either by subdural or by malarial therapy if treatment is begun at a sufficiently early stage. Gasteiger, on the other hand, is of the opinion not only that malaria is of no benefit but that its use is contraindicated because it occasionally causes a rapid reduction in the visual acuity. Magitot offers the interesting suggestion that syphilitic atrophy of the optic nerve (as well as other forms of primary or retrobulbar atrophy and of diffuse chorioretinitis) should be treated by sympathectomy of the nerve plexus surrounding the common carotid artery. The artery is decorticated for a distance of about 2 cm. up to the bulb of the internal carotid artery, and the carotid ganglion is removed. The two sides are operated on with a supervening interval of from ten to twenty-five days. The physiologic effect produced is a rise in the blood pressure in the peripheral portion of the circulatory system (in 25 per cent of patients), but more particularly there is an increase (permanent?) in the pressure in the retinal arteries and in the entire cerebral circulation, thus improving the blood supply to the diseased area. Magitot reports the cases of 3 patients with primary atrophy of the optic nerve due to syphilis. In the first vision increased from perception of movements of the hands to 1/25; in the second, from complete blindness to perception of light in the left eye and from 1/20 to 1/10 in the right eye, and in the third, from 1/10 (only the left eye affected?) to 4/10. The visual fields were enlarged in all cases. The exact duration of the improvement is not stated but does not exceed four months. In view of the gravity of primary atrophy of the optic nerve due to syphilis, this novel scheme of treatment is perhaps worthy of further trial.

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112. Schiff-Wertheimer: Pathogénie et traitement de l'atrophie optique tabétique, Bull. Soc. d'opht. de Paris, no. 8, November 1932, p. 1.

113. Gasteiger, H.: Zur Malariatherapie der tabischen Sehnervenatrophie, Arch. f. Augenh. **108**:471, 1934.

114. Magitot, A.: La sympathectomie carotidienne comme thérapeutique de certaines affections dégénératives du nerf optique et de la rétine, Bull. Acad. de méd., Paris **111**:816, 1934.

Acetarsone in the Treatment of Neurosyphilis.—Griggs and Schamberg [115] gave sodium acetarsone intravenously in a weekly dose of 1 Gm. and a total dose of from 8 to 20 Gm. to 17 patients with neurosyphilis. There were subjective improvement in the majority of instances, a noticeable tonic effect similar to that of tryparsamide, some serologic improvement in several cases and one instance of dimness of vision following the administration of the drug. The authors believe the method to be worthy of further trial.

Spiegel [116] has treated 25 patients by approximately the same method, giving the drug continuously at weekly or biweekly intervals, however, over a much longer period of time. He also is encouraged by the favorable results obtained.

Use of Tryparsamide in Treatment of Neurosyphilis.—Although the favorable effect of tryparsamide on neurosyphilis has been recognized since 1923, most of the available reports in the literature deal with early rather than late results; and interest in this powerful therapeutic agent has been less than that accorded to the more spectacular fever therapy with malaria and other agents. The survey of 81 patients with dementia paralytica treated with tryparsamide by Solomon and Epstein [117] between 1923 and 1930 and restudied in 1933 is therefore of particular value. In 42 per cent a clinical "arrest" (i. e., complete remission) was obtained, in 29 per cent the condition remained stationary and in 28 per cent no improvement was noted. While 14 of the 81 patients died during the period of observation, death was due to unarrested dementia paralytica in only 5, and the average duration of life was greatly prolonged in the living members of the series. The cerebrospinal fluid became normal in 37 per cent and was much improved in 16 per cent, moderately improved in 10 per cent and unimproved in 36 per cent. The period elapsing from the start of treatment to the time at which the spinal fluid became normal varied from one to nine years, and the number of injections of tryparsamide necessary to produce the same result varied from twenty to two hundred and thirty. No significant difference in results was found in patients receiving tryparsamide alone and those receiving other types of antisyphilitic treatment in addition to tryparsamide (except fever therapy). Seventeen patients of the series who did not respond satisfactorily to tryparsamide were subsequently given fever therapy with strikingly beneficial results. A comparison

115. Griggs, L. H., and Schamberg, J. F.: Acetarsone in the Treatment of Neurosyphilis, Arch. Dermat. & Syph. **20**:645 (May) 1934.

116. Spiegel, L.: Treatment of Neurosyphilis with Acetarsone (Stovarsol) Given Intravenously, Am. J. Syph. & Neurol. **18**:56, 1934.

117. Solomon, H. C., and Epstein, S. H.: Dementia Paralytica: Results of Treatment with Tryparsamide, Arch. Neurol. & Psychiat. **33**:1216 (June) 1935.

of these results with those obtained from treatment with malaria in 152 of the author's patients [118] showed no significant differences.

In my opinion, the ideal method of treatment of patients with dementia paralytica is first fever therapy, preferably malaria, followed by treatment with tryparsamide. It is distinctly encouraging to know that when malarial therapy is impracticable (as in patients in poor physical condition or, for reasons of immunity, in Negroes) a weapon of attack as powerful as tryparsamide is available.

Effect of Tryparsamide on the Eye.—In a paper based on the observation of too small a number of cases to be of value, Mayer and Smith [119] arrive at a conclusion diametrically opposite to that of most previous observers and state that tryparsamide does not exert an untoward effect on previously normal eyes. In a more adequate study, Lazar's [120] opinion is more in harmony with that of others. He concludes that experimentally there are no changes in the eye, optic nerve, chiasm or brain of lower animals or man which can be definitely attributed to the effects of tryparsamide. Nevertheless, a definite loss of vision immediately after the use of the drug leaves no doubt as to its toxic effect. Serious and even permanent visual damage may result even if the visual apparatus was previously normal, and the drug should not be administered to patients with preexisting atrophy of the optic nerve. The visual fields should be examined as a routine before the use of the drug is started, and this examination should be repeated when subjective visual difficulty becomes apparent or after from three to six injections have been given.

FEVER THERAPY

With the introduction of a series of new physical methods of producing artificial fever, interest in the subject continues. The Council on Physical Therapy of the American Medical Association [121] sounds a timely note of warning, as follows:

> The best method for administering artificial fever induced by physical agents . . . is not firmly established. . . . This method should be used only in hospitals, surrounded with the safeguards commonly employed in a major surgical operation, and under the direction of skilled physicians.

118. Solomon, H. C., and Epstein, S. H.: Dementia Paralytica: Results of Treatment with Malaria in Association with Other Forms of Therapy, Arch. Neurol. & Psychiat. **33**:1008 (May) 1935.

119. Mayer, L. L., and Smith, R. D.: Ocular Manifestations of Tryparsamide Treatment of Syphilis, Illinois M. J. **65**:258, 1934.

120. Lazar, N. K.: Effect of Tryparsamide on the Eye: An Experimental and Clinical Study and Report of Case, Arch. Ophth. **11**:240 (Feb.) 1934.

121. Hyperpyrexia Produced by Physical Agents, Report of Council on Physical Therapy, J. A. M. A. **103**:1308 (Oct. 27) 1934.

Bierman and Fishberg [122] summarize the physiologic changes which occur during this method of treatment. The velocity of the flow of blood is markedly accelerated, the pulse rate rises an average of 8.5 beats per minute for each degree Fahrenheit of elevation of temperature, the systolic blood pressure rises slightly and then falls slightly, and the diastolic pressure falls markedly. Sweating is profuse, but if fluids are freely given, the volume and viscosity of the blood remain unchanged. The respiratory rate rises, and periods of apnea occur. There is first leukopenia and later leukocytosis, due largely to the appearance of young neutrophils and immature forms of leukocytes. There are marked alkalosis and excessive excretion of chlorides (by ultrafiltration) and of lactic acid (by concentration) in the perspiration. The level of chlorides in the blood, urine and gastric juice is lowered. The titer of the complement-fixing antibodies of the blood in animals immunized against various bacteria falls temporarily.

Bishop, Lehman and Warren [123] compare the results of fever therapy utilizing diathermy, radiothermy and radiant energy (infrared rays) and express the belief that the clinical effect and results are the same. The use of radiant energy seems, however, to be the most convenient and economical of the three methods.

Mortimer and Osborne [124] see no advantage in the short wave diathermy apparatus over conventional diathermy and express their doubt as to the claims that there is specific bactericidal action of these high frequency currents.

Epstein and Cohen [125] review the literature and report the results of fever treatment in 33 patients with early syphilis. In 94 per cent of the patients spirochetes disappeared from open lesions following treatment with hyperpyrexia alone. Lesions healed, but in 3 patients prompt clinical recurrences developed after the cessation of treatment. Reversal of the serologic reactions was not obtained in any case. The authors conclude that hyperpyrexia alone is not a satisfactory method of treatment of early syphilis and interpret the failure as due to the impossibility of raising the temperature of the skin and mucosae to the thermal death point of the virus.

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122. Bierman, W., and Fishberg, E. H.: Some Physiologic Changes During Hyperpyrexia Induced by Physical Means, J. A. M. A. **103**:1354 (Nov. 3) 1934.

123. Bishop, F. W.; Lehman, E., and Warren, S. L.: A Comparison of Three Electrical Methods of Producing Artificial Hyperthermia, J. A. M. A. **104**:910 (March 16) 1935.

124. Mortimer, B., and Osborne, S. L.: Tissue Heating by Short Wave Diathermy, J. A. M. A. **104**:1413 (April 20) 1935.

125. Epstein, N. N., and Cohen, M.: The Effects of Hyperpyrexia Produced by Radiant Heat in Early Syphilis, J. A. M. A. **104**:883 (March 16) 1935.

Whether the association of heat and chemotherapy will prove to be of greater value in the treatment of early syphilis than chemotherapy alone, as suggested by the experimental studies and clinical trials of Richet and Dublineau,[126] can be determined only by further study. Probably the discomfort, loss of time and actual risk surrounding fever therapy will render it of limited application in patients with early syphilis, who after all are not incapacitated by their disease.

Mechanism of Action of Fever Therapy and of Chemotherapy in Syphilis.—Levaditi and his associates[127] tried the effect of short wave diathermy in spirillosis of the chicken, infection of the mouse with Trypanosoma Evansi, toxoplasmosis of the rabbit caused by Toxoplasma cuniculi, polyarthritis of the mouse due to Streptobacillus moniliformis, rabies, herpetic infection in the mouse, encephalitis in the mouse caused by the virus of venereal lymphopathy and experimental syphilis in the mouse and rabbit. On spirillosis of the chicken, recurrent fever of the rat and mouse, trypanosomiasis, rabies and polyarthritis and herpes of the mouse there was no effect. In about 50 per cent of cases of toxoplasmosis there was a favorable influence and in those of encephalitis due to the virus of venereal lymphopathy there was an inconstant favorable influence. Thus, on acute infections which are usually promptly fatal there was no effect.

In syphilis the curative and preventive action of fever therapy by short wave diathermy is incontestable. The authors started first by demonstrating that normally the temperature of the testicular chancre is constantly from 4 to 5 C. lower than the rectal temperature and that at the height of fever, when the rectal temperature is from 42 to 43 C., the highest temperature of the testicular syphiloma is 39.6 C. This is below the level which other authors have shown to be spirocheticidal in vivo or in vitro (41 to 42 C.).

The activity of fever therapy is shown by rapid healing of the chancre, by the disappearance of spirochetes, by morphologic modification of the remaining spirochetes, by sterilization of the lymph nodes and of the brain and finally by frequent negative reactions of serologic tests. Unhappily, however, these therapeutic and prophylactic effects are far from being constant. With difficulty one can prevent infection in from about 50 to 60 per cent of rabbits. In the mouse in spite of a great

126. Richet, C., Jr., and Dublineau, J.: Pyréto et chimiothérapie associées dans le traitement de le syphilis du lapin, J. de physiol. et de path. gén **31**:794, 1933. Richet, C.; Dublineau, J., and Joly, F.: Pyréto et chimiothérapie associées dans la syphilis primaire et sécondaire; étude expérimentale et clinique, Presse méd. **2**:649, 1933.

127. Levaditi, C.; de Rothschild, H., and others: Etude expérimentale de la thermothérapie générale par les radiations à ondes courtes, Ann. Inst. Pasteur **52**: 23, 1934.

number of treatments the lymph nodes continue to contain spirochetes, which are easily demonstrable on section and are virulent.

It is thus certain that an individual factor enters the picture in one sense or another to influence the curative or preventive activity of treatment with heat. Success depends on the individual patient, the moment of starting treatment and the degree of the morbid process. Thus, short wave irradiation and probably also fever treatment in general act not directly in suppressing the pathogenic activity of the organism of the disease but indirectly by the intermediation of the organism which harbors this agent. The heat either facilitates or provokes sterilization by augmenting the defensive ability of the humoral or cellular mechanism which the organism brings into play toward spontaneous cure. In this respect fever treatment does not differ from chemotherapy. Modern research tends to confirm more and more the conception formulated by Levaditi in 1908 to the effect that chemotherapeutic agents play the rôle of catalyzers in respect to the principles which insure the destruction of germs and the sterilization of the tissues. Heat may be one of the active factors, but it is not all. Other curative elements enter in of which nothing is known, but which physiologic and physical investigation will some day disclose. Whatever may be the mechanism of heat treatment by short wave diathermy, its activity is far less under the circumstances of these experiments than that of various drugs.

In a speculative discussion Dustin [128] arrives at similar conclusions as to the chemotherapy of syphilis. Ehrlich expressed his belief in the direct toxic action of drugs on the parasite. Modern investigators, however, consider that this explanation is too simple and that the pharmacodynamic action of drugs is due to the inciting of complex humoral and cellular mechanisms. The principal objection to the simple explanation rests in the fact that in vivo the drug is present in a dilution so considerable that it is completely inactive on parasites studied in vitro. From this fact it is necessary to deduce as a working hypothesis that the parasiticidal action of a drug results not from direct parasitotropism but from the production of new substances from the combination or from the conflict of the injected drug with different albumins in the body.

In a long series of remarkable papers Levaditi and his collaborators have produced important facts bearing on this hypothesis. In 1905 Levaditi showed that sodium arsanilate is incapable of destroying trypanosomes in vitro but becomes very active after incubation with a fresh extract of rabbit liver. An arsenicalized toxalbumin is manu-

128. Dustin, A. P.: Quelques aperçus anatomo-pathologiques sur le mode d'action des produits chimiothérapeutiques, Bruxelles-méd. **13**:1035, 1933.

factured by the organism at the expense of the arsenic. This derivative which is so active in vitro is, however, void of preventive or curative action in vivo. This difference is apparently due to the fact that the newly formed substance has a great affinity for a series of tissues on which it fixes itself, particularly red blood cells, liver and spermatozoids. Similar results have been obtained with antimony, bismuth and tryparsamide. The lysis of the spirochete demands only infinitesimal traces of metal.

Dustin says that the action of certain chemical substances and that of radiation are identical in that neither is direct. The chemicals are much less active on cells or organisms observed in vitro or on tissues the blood supply of which is temporarily interrupted or reduced by epinephrine.

The discovery of the reticulo-endothelial system enters into this discussion. This system is present throughout the entire organism, is more abundant at certain points (connective tissue, the sinusoids of the liver, lymph glands, spleen and bone marrow) and possesses the fundamental property of taking up and holding fine particles in suspension, particularly those of exogenous origin (such as india ink, carmine, pyrrol blue or a bacterial suspension) or of endogenous origin (such as hemosiderin, lipoids and pigments). These cells that are capable of fixing noxious substances or bacterial suspensions should play a prime rôle in the defense of the organism against infections and in the development of the phenomena of immunity. The extraordinary success which has met this conception and the enormous amount of work which has been done on it are well known. However, this conception leaves a good deal to be desired.

In 1923 Bieling noted that the formation of antibodies was greatly diminished in splenectomized animals on blockage with saccharate of iron. In 1927 Kritchevsky noted that blockage in the mouse diminished the action of the arsenicals. In the same year Jungenbluth found that in mice in which there had been blockage with saccharate of iron, infection with spirochetes or trypanosomes was much more grave and more resistant to treatment. Feldt and Schott obtained similar results, though others, for example Schlossberger and Prigge, expressed the opinion that the reticulo-endothelial system played no rôle in the action of the drug. Collon has shown that so-called blockade of the reticulo-endothelial system is without effect on the development of immunity, on the reserve of alexin or on the formation of precipitous agglutinins, hemo-agglutinins or antitoxins. Dustin is of the opinion that the influence of the reticulo-endothelial system has been exaggerated and that a great deal more work is necessary on this point.

Dustin has worked experimentally with the thymus gland in a number of different animals and for a number of different purposes; but in the course of these experiments he has noted that animals treated with drugs, including the arsenicals, showed very interesting changes in the thymus gland and in the lymph nodes, spleen and tonsils. Histologic studies of the organs after treatment with these drugs showed the destruction of an enormous number of cells, the appearance of phagocytes and intracellular digestion of the débris and presumably the liberation of nucleolytic ferments and a whole series of products of disintegration not well known, and in addition important disturbances of the mitotic rhythm—sometimes by violent excitation of cell division, sometimes by too prolonged suspension. These cellular changes may play a very great part in the chemotherapeutic activity of injected drugs.

In spite of the suggestion conveyed by Dustin's work and in the literature cited by him that the reticulo-endothelial system influences the effect of antisyphilitic drugs, Pockels,[129] working in Kolle's laboratory, was unable to confirm this hypothesis. He conducted an elaborate series of experiments involving trypanosomal and spirochetal infections in mice and rabbits and interference with the reticulo-endothelial system by various procedures, none of which had any demonstrable effect on the therapeutic activity of the arsphenamines.

These three studies are cited at length because they illustrate the uncertain basis of the present knowledge of the mechanism of treatment in syphilis and the trend of opinion in the direction that a larger part of that effect consists in the stimulation of the patient's own power of defense.

The Physiology of Electropyrexia.—In an effort to explain why the fever treatment of syphilis is often successful in the late stages but is not in the early stages, Neymann and Osborne[130] determined by means of specially contrived instruments that artificial fever raises the temperature of internal organs (liver, cisterna magna, spinal canal, rectum and colon) 2 F. higher than the subcutaneous temperature of the thorax and abdomen and that in the extremities the subcutaneous temperature is proportionately even lower. Since the thermal death point of Spirochaeta pallida is 42 C. (107.6 F.) maintained for from one to six hours, since internal temperatures of 109.6 F. are not practicable in human beings and since in early syphilis the virus is abundantly present in the

129. Pockels, W.: Experimentelle Studien über die Wirkung des Retikuloendothels auf die Toxizität und die Heilwirkung der Arsenobenzole, Arb. a. d. Staatsinst. f. exper. Therap. **29**:12, 1934.

130. Neymann, C. A., and Osborne, S. L.: The Physiology of Electropyrexia, Am. J. Syph. & Neurol. **18**:28, 1934.

skin and superficial mucosae, the poor results of fever therapy in the early stages of syphilis are readily explained.

In addition, these authors point out that during the induction of artificial fever there is a marked loss of fluids and chlorides owing to perspiration. The administration of sweat-inhibiting drugs causes delirium; the basal metabolic rate rises an average of 7 per cent for each degree Fahrenheit of increase in temperature; there are concentration of the body fluids and a consequent increase in red and white blood cells and in the nonprotein nitrogen and uric acid contents of the blood during fever, and the systolic blood pressure rises and the diastolic pressure falls.

Fever Therapy of Neurosyphilis with Vaccine.—Schnitker [131] reports that in 25 patients the use of typhoid H antigen vaccine combined with tryparsamide produced symptomatic and serologic improvement comparable to that obtained by other forms of fever therapy. The interest of this paper lies in the pyrogenic agent used—"a water-clear saline filtrate containing the flagellar (H) antigen of the organism, the somatic (O) antigen having been blocked by phenol." The paroxysm of fever produced by it is relatively constant in all persons. It differs from that of whole typhoid vaccine in that the rise of temperature is more constant, slightly higher and more prolonged, and it has the special advantage of being less violent (i. e., the patients are not nearly so sick).

Fever Treatment of Dementia Paralytica.—Cullins, Morgan and Seymour [132] express the belief (on the basis of 205 patients treated) that diathermy treatment of dementia paralytica is less satisfactory than induced malaria, but that mechanical fever has a distinct place in therapy, second only to that of malaria.

Results of Malarial Therapy of Neurosyphilis.—The most interesting and satisfactory reports of the results of malarial therapy of neurosyphilis appearing in recent months are those of Freeman, Eldridge and Hall,[133] O'Leary and Welsh [134] and O'Leary.[135]

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131. Schnitker, M. T.: Treatment of Dementia Paralytica with Typhoid H Antigen Vaccine, Arch. Neurol. & Psychiat. **31**:579 (March) 1934.

132. Cullins, J. G.; Morgan, H. P., and Seymour, W.: Superdiathermy in Treatment of Dementia Paralytica, M. Bull. Vet. Admin. **11**:217, 1935.

133. Freeman, W.; Eldridge, W. W., and Hall, R. W.: Malaria Treatment of Dementia Paralytica: Results in Two Hundred and Five Cases After Five to Eleven Years, South. M. J. **27**:122, 1934.

134. O'Leary, P. A., and Welsh, A. L.: Treatment of Neurosyphilis with Malaria: Observations on 984 Cases in the Last Nine Years, J. A. M. A. **101**: 498 (Aug. 12) 1933.

135. O'Leary, P. A.: Asymptomatic Neurosyphilis, South. M. J. **28**:47, 1935; Malaria Therapy in Asymptomatic Neurosyphilis, Ann. Int. Med. **7**:1513, 1934.

Freeman and his co-workers followed up 195 of a series of 205 patients treated for dementia paralytica for from five to eleven years after the completion of malarial treatment. Of those traced, 31 per cent were discharged from the hospital (i. e., in complete or nearly complete remissions), 39 per cent remained hospitalized and 30 per cent died. The remissions obtained showed indications of being permanent, and the percentage of recoveries has not declined notably with the passage of years. The good results obtained were in reasonably direct proportion to the number of paroxysms of fever, and the authors express the belief not only that less than ten paroxysms are relatively futile but that as many paroxysms as the patient can safely tolerate should be allowed.

O'Leary and Welsh report on the status of patients treated with malaria who had a wide variety of types of neurosyphilis. Excellent clinical results were obtained as follows: advanced dementia paralytica, 35 per cent; early dementia paralytica, 46 per cent; asymptomatic neurosyphilis with the "paretic formula" in the cerebrospinal fluid ("asymptomatic paresis"), 78 per cent; tabetic dementia paralytica, 55 per cent; tabes dorsalis (general group), 42 per cent; gastric crises with negative reactions of the cerebrospinal fluid, 31 per cent; intractable lightning pains with negative reactions of the spinal fluid, 11 per cent, and primary atrophy of the optic nerve, 14 per cent. The authors express the belief that malarial treatment is indicated not only for patients with dementia paralytica but also and particularly for patients with other forms of syphilis who are not responding favorably to other types of antisyphilitic treatment.

O'Leary was especially impressed with the value of malarial treatment in 89 cases of asymptomatic neurosyphilis, and in two communications he points out that in 50 per cent of patients whose spinal fluid fails to become normal after therapy with arsphenamine, bismuth, mercury and subdural injections, serologic normality (apparently permanent) may be achieved by means of malarial treatment. Fever therapy is therefore of the utmost value in the prevention of parenchymatous neurosyphilis as well as in its treatment.

Malarial Therapy.—The relationship of blood grouping to induced malaria is discussed by Polayes and Derby [136] on the basis of a review of the literature and personal experience with 127 patients. When the donor's blood is compatible, the incubation period of malaria in the recipient is halved (to an average of four and three-tenth days). The question of minor reactions of incompatibility and of so-called primary fever (i. e., remittent fever preceding the development of frank paroxysms) also are discussed.

136. Polayes, S. H., and Derby, I. M.: Blood Groups and Therapeutic Malaria, J. A. M. A. **102**:1126 (April 7) 1934.

The Reactivation of Malaria.—Every physician who treats patients with neurosyphilis is familiar with the premature spontaneous abortion of induced tertian malaria which occurs, depending on the strain employed, in from 5 to 10 per cent of patients treated. Epinephrine, typhoid vaccine given intravenously and cold baths have been used with varying success in the attempt to reactivate the paroxysms of fever in such patients. Videla,[137] working with natural and induced malaria, was successful in reactivating a latent infection in 4 of 6 patients by means of the daily intravenous injection of 10 cc. of a 10 per cent solution of calcium chloride (from one to three injections were necessary). The mechanism by which this result is produced is not clear, but the method is worthy of further trial.

The Untoward Effects of Malarial Therapy.—Karnosh and Williams[138] review the complications of malarial therapy in 580 patients with dementia paralytica and describe an untoward sequel not heretofore stressed, characterized by hemorrhages, hematomas and noninflammatory ulcers of the intestine, which they regard as specific lesions due to malaria. This complication occurred in 5 patients, all of whom died, and in each the specific lesion was found at necropsy. Shirokogorov[139] studied the interrelationship between malaria and pulmonary tuberculosis at necropsies on 800 patients who had died of acute or chronic malaria (not induced) and found no evidence that malaria reactivated a primary tuberculous focus.

The Treatment of Malaria.—Craig[140] provides a review of the present status of atabrine (an acridine derivative) and plasmochin (N-di-ethylamino-iso-pentyl-8-amino-6-methoxyquinoline), which will be valuable to all physicians utilizing malarial therapy.

MAPHARSEN

"Mapharsen" is the producer's name for meta-amino-para-hydroxyphenylarsine oxide. This drug, an exceedingly potent and toxic arsenical, was studied by Ehrlich and abandoned because of its toxicity. It is considered to be the therapeutically effective breakdown product of all of the arsphenamines. Experimental and clinical study of this interesting drug has been taken up afresh by the Wisconsin group of investi-

137. Videla, C. A.: Reactivation of Latent Malaria by Calcium Chloride Injections, Prensa méd. argent. **21**:2378, 1934.

138. Karnosh, L. J., and Williams, G. H.: Some Unusual Complications in Malaria Therapy, Ohio State M. J. **31**:193, 1935.

139. Shirokogorov, I. I.: Effect of Malaria on Pulmonary Tuberculosis, Klin. med. **12**:1786, 1934.

140. Craig, C. F.: Results of Recent Research in the Treatment of Malaria, South. M. J. **27**:546, 1934.

gators. To date only a portion of their experimental work has been published. Tatum and Cooper [141] show that this drug is a pure chemical preparation the purity of which is readily determinable by chemical methods, whereas the arsphenamines are chemical mixtures which may vary with each lot and therefore require biologic assay. Mapharsen increases in toxicity only slowly on oxidation. The minimum lethal dose and minimum tolerated dose, respectively, for various animals are as follows: rats, 25 and 20 mg. per kilogram of body weight; rabbits, 16 and 10 mg.; cats, 7 and 5 mg., and dogs, 15 and 10 mg. For infection of rats with Trypanosoma equiperdum the curative dose is 0.8 mg. per kilogram and the therapeutic index 25. For T. rhodesiense infections of rats the curative dose is 9 mg. per kilogram and the therapeutic index 2.2. A single dose of 6 mg. per kilogram (therapeutic index, 1.6) or three weekly injections of 0.8 mg. per kilogram (index, 12.5) is curative of rabbit syphilis. These indexes for rabbit syphilis were superior to those of two brands of neoarsphenamine studied by the same investigators. The authors are convinced that mapharsen possesses such outstanding advantages over the arsphenamines as to justify its clinical investigation. This clinical trial has been under way for several years, and the results of the use of the drug in human beings will be published shortly.

141. Tatum, A. L., and Cooper, G. A.: An Experimental Study of Mapharsen (Meta-Amino-Para-Hydroxy Phenyl Arsine Oxide) as an Antisyphilitic Agent, J. Pharmacol. & Exper. Therap. **50**:198, 1934.

CORRECTION

In the article by Dr. Walter M. Boothby, entitled, "Disease of the Thyroid Gland: An Interpretative Review of Progress Toward Solution of the Problem," in the July issue (ARCH. INT. MED. **56**:136, 1935), "approximately 25 mg." in the thirteenth line on page 160 and in the tenth line on page 161 should read "approximately 250 mg."

Book Reviews

The Clinical Aspects of Visceral Neurology, with Special Reference to the Surgery of the Sympathetic Nervous System. By W. K. Livingston, M.D., Clinical Associate in Surgery, University of Oregon Medical School. Cloth. Price, $5. Pp. 246, with 46 illustrations and 3 color plates. Springfield, Ill.: Charles C. Thomas, Publisher, 1935.

This book gives a brief review of the anatomy, physiology and clinical aspects of visceral surgery but, as the name implies, is written chiefly from the point of view of the surgeon with respect to sympathetic surgery. The physiologic aspect of both the normal control of the peripheral circulation and the late effects of sympathectomy are not treated sufficiently to give the reader a clear conception of these complex processes. There is some discussion regarding the skin temperature as a test of circulation, but Livingston does not impress on the reader that at best the skin temperature can be only a rough approximation of circulation, as it is well known that the skin temperature represents the sum total of a number of factors acting on the skin, of which circulation is only one. Failure to appreciate this fact and the ease of taking the skin temperature has led to unwarranted conclusions. In the discussion of poor results from sympathetic surgery in some cases of Raynaud's disease it is implied that the operation was incomplete. There is good evidence to show that in both lower animals and man the circulation of the part returns to the preoperative level in a comparatively short time after sympathetic ganglionectomy and ramisectomy, even though the operation is complete. Livingston has not thoroughly considered the factors which control the vascular tone in the absence of sympathetic vasoconstrictor tone. However, the criticisms and unfavorable impressions may have been gained from the fact that the author has attempted to cover such a tremendous and controversial field in such a small volume. The known facts regarding sympathectomy for relief of peripheral symptoms indicate that this type of surgical intervention must still be considered purely an experimental procedure. This book cannot be recommended as contributing anything but the surgical point of view of visceral surgery, but it may serve as a good outline for those interested in this field.

Chemistry of the Hormones. By Benjamin Harrow, Associate Professor of Chemistry, the City College, College of the City of New York, and Carl P. Sherwin, St. Vincent's Hospital and French Hospital, New York. Price, $2.50. Pp. 227. Baltimore: Williams & Wilkins Company, 1934.

This book is primarily for the biochemist who wishes for a survey of the best methods for the preparation of hormones. It is not exhaustive in its treatment, but rather gives a few of the most successful methods of preparation. The reader becomes acqainted with the present state of the chemistry of hormones without the confusion which may follow when the subject is presented in detail.

Some historical material is included. The physiologic properties of the hormones are touched on briefly. There is little discussion of clinical material, and only the most significant papers are included in the bibliography.

The work is primarily a reference book. The type is large, well arranged and very readable.